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## CASE REPORT

## Severe lead toxicity attributed to bullet fragments retained in soft tissue

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**SUMMARY**

A man aged 30 years presented to an emergency department with a 1 month history of severe abdominal pain, jaundice, constipation, lower extremity weakness and weight loss. A peripheral blood smear was performed that showed basophilic stippling of erythrocytes prompting a blood lead level (BLL) evaluation. The patient had a BLL of >200 µg/dL. Retained bullet fragments were identified in the left lower extremity from a previous gunshot wound 10 years prior. Lead from the excised bullet fragment was consistent with the patient's blood lead by isotope ratio analysis. This case is a rare example of a severely elevated BLL attributed to bullet fragments in soft tissue. Bullets retained in soft tissue are not often considered a risk factor for a markedly elevated BLL because they become encapsulated within the tissue over time.

**BACKGROUND**

Lead (Pb) toxicity attributable to retained bullets is an infrequently reported but important cause of Pb toxicity. Approximately 115 000 firearm injuries occur annually in the USA,<sup>1</sup> of which ~70% are non-fatal.<sup>1</sup> Depending on location and other clinical considerations retained bullets are not routinely removed<sup>2</sup> and typically contain 50–100% Pb.<sup>3</sup> The diagnosis of elevated blood lead level (BLL) because of a retained bullet is challenging. Symptoms are often non-specific with onset occurring days or decades after initial injury. In addition, an elevated BLL in a patient with a retained bullet often cannot be definitively attributed to the bullet, because of exposures to Pb from other sources. Further investigation of the exposure source is often required.<sup>4</sup>

The majority of Pb toxicity cases from retained bullets are only discovered when patients' symptoms become severe.<sup>3</sup> Elevated BLLs are most common when bullet fragments are retained in areas with continuous fluid bathing (eg, synovial fluid of knee or hip joints) and highly vascular tissues (eg, bone).<sup>5</sup> When the bullet is retained in soft tissues such as the muscle, encapsulation usually prevents Pb dissolution and systemic absorption of the metal.<sup>3</sup> We present an unusual case of severe Pb intoxication from bullet fragments retained in soft tissue. A man aged 30 years was diagnosed with systemic Pb toxicity ~10 years after a gunshot wound to the left lower extremity with retention of bullet fragments in the soft tissues. Epidemiological investigation and Pb isotopic analysis confirmed the fragments to be the exposure source.

**CASE PRESENTATION**

In August 2015, a previously healthy man aged 30 years presented to an emergency department in hospital B reporting ~1 month of severe abdominal pain, jaundice, constipation, lower extremity weakness and an unintentional weight loss of 18 kg. Prior to visiting hospital B, the patient was hospitalised for 2.5 weeks in hospital A for similar symptoms, but the evaluation failed to determine any aetiology. Initial laboratory studies at hospital B revealed leucocytosis (14.2×10<sup>3</sup> white cell count (WCC)/µL, normal: 4–10×10<sup>3</sup> WCC/µL), low haemoglobin (9.1 g/dL, normal: 13–17 g/dL) and elevated total bilirubin (6.2 mg/dL, normal: 0.2–1.0 mg/dL). The haematological service was consulted and determined that the patient had haemolytic anaemia and was glucose-6-phosphate dehydrogenase deficient. A peripheral blood smear was performed that showed basophilic stippling of erythrocytes prompting a BLL evaluation. BLL and zinc protoporphyrin (ZnPP) levels were assessed on day 10 of hospitalisation. The venous BLL>200 µg/mL is considered severe. The ZnPP level was >600 µg/dL and represents that this was not an acute ingestion and had some length of chronic exposure to serum Pb levels of at least 25–30 µg/dL.<sup>6,7</sup> Elevated BLLs are reportable in Wisconsin. If a test result is >25 µg/dL the Wisconsin Department of Health Services (DHS) contacts the individual and administers a standard questionnaire to identify the source of the exposure. Preliminary results of the epidemiological investigation conducted with assistance from local and state public health staff revealed no obvious Pb exposure source. On further interview, the patient recalled sustaining a gunshot wound to the left lower extremity ~10 years back. Initially after the injury, the retained bullet (or part thereof) could be felt under the skin of his thigh. The patient had been in a car accident ~1 month before symptoms onset. He reported that after the accident the bullet could no longer be felt under the skin of his thigh, consistent with fragment migration. Radiographs of the left lower extremity (figure 1) revealed metallic foreign bodies in the posterolateral soft tissues of the distal thigh with calcification and reactive change without any underlying bony abnormality.

**METHODS****Epidemiological investigation**

To investigate possible Pb exposure sources, a standard telephone questionnaire was administered by DHS staff, which is a routine process for BLLs >25 µg/dL. Detailed information concerning



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**Figure 1** Radiographic views of patient's femur. Lateral (panel A) and anteroposterior (panel B) views of left femur; metallic foreign bodies are visible in the posterior lateral soft tissues of the distal thigh suggesting prior gunshot wound and surrounding calcification and reactive change. No underlying bony abnormalities are seen.

pertinent patient history, symptoms and course of illness was obtained from in-person interviews with patient and his partner. Multiple, consecutive blood samples were obtained from the patient and his son and tested for Pb. In addition, Pb analysis was performed on paint samples collected during an investigation of the patient's residence.

### Pb isotopic analysis

Pb isotopic ratio analysis was performed on environmental samples from the patient's home, retained bullet and blood samples from the patient and his child, aged 1 year. For each sample, multicollector-inductively coupled plasma mass spectrometry (MC-ICPMS) was used to analyse the purified Pb fractions of the digested samples. Concentrations of the stable Pb isotopes  $^{206}\text{Pb}$ ,  $^{207}\text{Pb}$ , and  $^{208}\text{Pb}$  were measured and expressed as ratios relative to concentrations of non-radiogenic  $^{204}\text{Pb}$ . In general, samples with results that match within error (the extent of which depends on the accuracy and precision of the sample preparation and analytical methods used) of one another are considered to have the same Pb source contributing to the final isotopic Pb signature.<sup>8</sup>

### DIFFERENTIAL DIAGNOSIS

After a thorough medical history and careful physical examination, the differential diagnoses for jaundice were gallbladder disease, drug allergy or cancer. The haemolytic anaemia pointed to sickle cell disease or gastrointestinal bleeding. Finally, constipation or the possibility of an abscess was differential diagnoses for abdominal pain.

### TREATMENT

On day 11 of hospitalisation the patient began a chelation regimen with dimercaprol (British anti-Lewisite, BAL) followed

by calcium disodium edetate ( $\text{CaNa}_2\text{EDTA}$ ). With chelation treatment, a rapid drop in serum BLL was seen as expected; the BLL decreased from  $114.9\ \mu\text{g/dL}$  on hospital day 12 and reached  $53.2\ \mu\text{g/dL}$  on day 15 of hospitalisation. Treatment was then changed to dimercaptosuccinic acid (DMSA), an oral chelating agent. The patient underwent surgery on day 18 of hospitalisation to remove the bullet fragments. During surgical exploration of the upper left leg, a thickened capsule was identified and opened. Aspiration of the capsule revealed 30 mL of thick, dark fluid and the major bullet fragment was removed from the evacuated capsule.

The patient demonstrated continued clinical improvement after chelation chemotherapy and surgical debridement, tolerating ambulation and diet. He was discharged in improved condition on day 24 of hospitalisation with a plan for continuing DMSA treatment for multiple weeks. Two months post-discharge, his BLL was  $78.2\ \mu\text{g/dL}$ , which was still elevated and warranted further treatment. The patient did not follow-up on his clinical appointments and was lost to follow-up.

### OUTCOME AND FOLLOW-UP

#### Results of epidemiological investigation

Pb concentration was  $>200\ \mu\text{g/dL}$  in the patient's initial serum sample and  $10\ \mu\text{g/dL}$  in a serum sample from the patient's son. The son's BLL is considered elevated and warrants further surveillance of BLLs but would not require medical work up or intervention unless further levels were  $>15\ \mu\text{g/dL}$  and chelation therapy is not warranted until  $45\ \mu\text{g/dL}$ . A severe elevation in BLL is considered  $>70\ \mu\text{g/dL}$  and warrants hospitalisation for parenteral chelation.<sup>7</sup> Interviews of household contacts provided additional information regarding the course of the patient's illness, but did not indicate sources of occupational or recreational exposures to Pb. Environmental samples did identify the

presence of Pb in the home. Paint samples from a door and window in the home showed 2.7% and 3.1% Pb, respectively. The paint samples consisted of several layers of multiple colours of paint, including white. The US Consumer Product Safety Commission has limited the allowable amount of Pb in house paint to <0.06%.<sup>9</sup>

### Results of Pb isotopic analysis

MC-ICPMS demonstrated high levels of correlation between Pb isotopes in the patient's blood and in the retained bullet (figure 2) matching within 0.007–0.049%, a difference detectable only because of the use of the MC-ICPMS capabilities. Ratios of  $^{206}\text{Pb}/^{204}\text{Pb}$  were 19.4449 ( $\pm 0.0006$ ) and 19.4538 ( $\pm 0.0009$ ) for the patient's blood and the retained bullet, respectively. Ratios of  $^{207}\text{Pb}/^{204}\text{Pb}$  for the patient's blood and the bullet were 15.7139 ( $\pm 0.0005$ ) and 15.7117 ( $\pm 0.0007$ ), respectively. In contrast,  $^{206}\text{Pb}/^{204}\text{Pb}$  and  $^{207}\text{Pb}/^{204}\text{Pb}$  ratios for the window paint were 18.8429 ( $\pm 0.0006$ ) and 15.6489 ( $\pm 0.0005$ ), respectively. For the door paint, the  $^{206}\text{Pb}/^{204}\text{Pb}$  ratio was 18.5114 ( $\pm 0.0005$ ) and the  $^{207}\text{Pb}/^{204}\text{Pb}$  was 15.6236 ( $\pm 0.0005$ ). Isotopic Pb ratios for the child's blood were poorly correlated to all other samples, to such an extent that they are considered having distinctly different Pb isotopic fingerprints, as displayed in figure 2.

### DISCUSSION

As of 2004, fewer than 100 cases of Pb toxicity caused by retained bullets had been reported in the medical literature.<sup>10 11</sup> However, in the USA during 2003–2012, a total of 457 cases of BLLs  $\geq 10$   $\mu\text{g}/\text{dL}$  in patients with retained bullets were identified by the Adult Blood Lead Epidemiology Surveillance (ABLES) programme.<sup>12</sup> Research has shown decreased renal function associated with BLLs as low as 5  $\mu\text{g}/\text{dL}$  and under, and increased risk for hypertension and essential tremor at BLLs <10  $\mu\text{g}/\text{dL}$ .<sup>13</sup> Considering the substantial number of injuries sustained from firearms each year, elevated

BLLs among patients with retained bullets might be underdiagnosed and under-reported. Only patients with substantial toxicity will likely be motivated to seek care and low levels of suspicion by medical providers might cause a delay in diagnosis.<sup>3</sup>

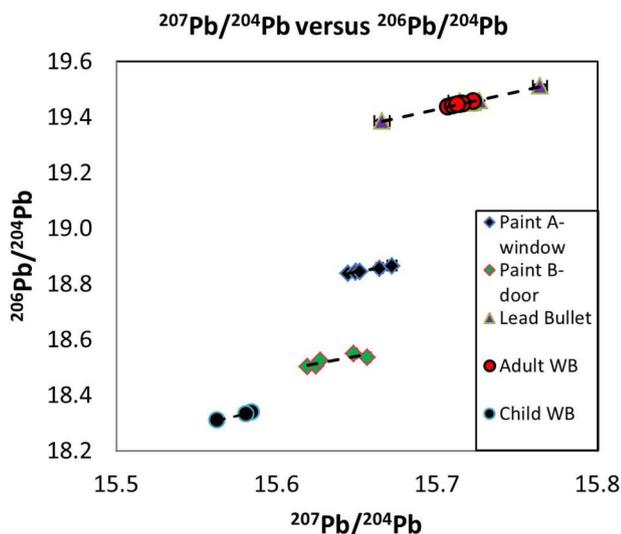
Pb toxicity has an insidious onset and patients with Pb toxicity because of retained bullets pose a diagnostic challenge. Several case reports of elevated BLL because of retained bullets indicate that patients with retained bullets often presented with non-specific symptoms months to decades after bullet retention.<sup>11</sup> Patients can present with abdominal pain, anorexia, constipation, lethargy, encephalopathy, cognitive dysfunction, peripheral neuropathy, hypertension, renal disease or seizures.<sup>11–15</sup> Classic indicators of Pb toxicity, including Pb lines between the teeth and gums, radiographic changes, elevated erythrocyte protoporphyrin levels and basophilic stippling of erythrocytes can prompt further testing, but have been reported to be non-specific and insensitive among certain populations.<sup>16 17</sup> In this case, the choice of ZnPP as opposed to free protoporphyrin or ZnPP/haem ratio was based on hospital laboratory availability. The results may also have been confounded by the patient's haemolytic anaemia but have been included for completeness.

Treatment for Pb toxicity because of retained bullets consists of chelation therapy and, in certain cases, surgical removal of bullet fragments. Previous reports have shown a substantial decline in BLLs after surgical removal of fragments.<sup>18 19</sup> However, the risk–benefit ratio of surgical intervention for fragment removal, varies among patients. In this patient, it is uncertain whether removal of the bullet fragment contributed to the observed decrease in BLL.

Although intravenous chelation therapy is indicated for severe Pb toxicity or substantial BLL elevations such as observed in this patient, it has limitations. Effects are generally confined to plasma and extracellular fluid compartments, leading to only a minor portion of total body Pb burden being removed.<sup>20</sup> Initiation of chelation therapy does result in a rapid decrease in the serum BLL and might resolve acute symptoms; however, its effect on long-term outcomes is unclear.<sup>20–22</sup>

Although acute symptoms in adults can resolve after chelation, limited information is available in the medical literature about long-term benefits.<sup>13 23 24</sup> Benefits of chelation might be questioned, because of the risk for adverse effects in a setting of uncertain benefits for long-term outcomes, organ toxicity and total Pb burden. Certain guidelines recommend chelation therapy for adult asymptomatic patients only when BLLs are >100  $\mu\text{g}/\text{dL}$ .<sup>25 26</sup> The decision to treat asymptomatic persons is largely at provider and patient discretion, and consultation with a toxicologist or experienced provider to aid in decision-making is recommended.<sup>25</sup>

When significant toxicity (eg, encephalopathy) is exhibited or Pb levels are >100  $\mu\text{g}/\text{dL}$ , parenteral chelating agents are indicated as first-line treatment.<sup>27</sup> The intravenous chelation agent used in the USA is  $\text{CaNa}_2$  EDTA, which can be started in conjunction with intramuscular BAL and continued for 3–5 days followed by oral chelation therapy with DMSA. There is no evidence-based consensus on how aggressively to treat Pb poisoned adults in regard to number or choice of chelating agents. It is recommended by some that use of BAL should be in combination with intravenous  $\text{CaNa}_2$  EDTA.<sup>28</sup> Use of BAL can cause pain with intramuscular injection and has an unfavourable adverse effect profile making  $\text{CaNa}_2$  EDTA is more convenient to use. Consultation with a toxicologist experienced in chelation is recommended. The need for repeated chelation regimens is



**Figure 2** Isotope ratio plot. Isotope ratio plot ( $^{207}\text{Pb}/^{204}\text{Pb}$  vs  $^{206}\text{Pb}/^{204}\text{Pb}$ ) of WB from an adult and child with elevated BLLs and several Pb sources including two paint samples from the home of the patients (Milwaukee, Wisconsin, USA), and a Pb bullet fragment surgically removed from the left thigh of the adult. Uncertainties are reported as  $2 \times$  the SE. The dotted lines represent linear regression lines. BLL, blood lead level; Pb, lead; WB, whole blood.

usually determined by postchelation BLL and presence of symptoms. Case reports support oral chelation therapy in systemic Pb bullet toxicity in combination with surgical debridement.<sup>27</sup> The initial BLL decline in this patient was transient, and BLL increased after hospital discharge despite continued chelation therapy. This is consistent with previous cases in which an increase in the BLL after chelation therapy cessation has been observed,<sup>21</sup> likely because of Pb released from bone. Bullet fragmentation and location of Pb fragments in joints and bone have been associated with higher BLLs.<sup>5</sup> In similar cases reported in the literature, retained bullet fragments often communicate with synovial or intervertebral disc spaces.<sup>11</sup> This case report indicated, as confirmed through our epidemiological investigation and isotopic analysis, bullet retention in soft tissues can also cause critically high BLLs. Of note, the patient had reported a recent motor vehicle collision and a change in the tactile consistency of the area of the thigh where the bullet had previously been palpable. Disruption of the fibrotic capsule enveloping the bullet, as might have occurred in this case, can result in bullet migration and Pb exposure.

### Learning points

- ▶ This case was a rare occurrence of elevated blood lead level (BLL) attributed to bullet fragments embedded in soft tissue.
- ▶ Chelation therapy in consultation with a local poison centre in combination with surgical removal of one of multiple bullet fragments was successful in reducing the patient's BLL.
- ▶ Collaboration with the local health department allowed detailed investigation of lead exposures and laboratory analyses that helped confirm the patient's lead exposure source.
- ▶ This case highlights potential risk for lead toxicity among patients with bullets retained in soft tissue.
- ▶ A management strategy including periodic BLL testing and radiographic imaging might be considered for patients with retained bullets, regardless of bullet location.

**Collaborators** Carrie D Tomasallo, Jon G Meiman, Martin M Shafer and Henry A Anderson.

**Competing interests** None declared.

**Patient consent** Obtained.

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