Hepatic Morphopathologic Findings of Lead Poisoning in a Drug Addict: a Case Report

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Abstract

We describe the case of a 40-year old Iranian man who was admitted to our hospital with severe abdominal pain, abnormal liver function tests and normocytic anemia. Suffering from multiple sclerosis, he was a regular user of opium for pain relief. Basophilic stippling of erythrocytes pointed towards the diagnosis of lead intoxication, the most likely source being contaminated Iranian opium. Serum lead and zinc protoporphyrin levels were strongly elevated. To assess the hepatotoxic effects of lead poisoning a liver biopsy was performed. Pathomorphologic findings of hepatotoxicity, rarely reported in humans, included active hepatitis together with extensive microvesicular and macrovesicular steatosis, hemosiderosis and cholestasis, and a lymphocytic cholangitis. Whilst treated with chelating therapy, liver enzymes returned to normal, suggesting reversibility of the histological findings.

Key words

Liver biopsy – opium – Iran – hepatotoxicity.

Introduction

Lead poisoning is a medical condition also known as saturnism or plumbism. It is caused by occupational or environmental exposure to sources of (in)organic lead. The most common sources are lead-containing paint, water, leaded pipes from public water supply, Asian herbal remedies, lead-glazed ceramics, and lead shot game [1]. Prevalence in the general adult population is unclear and especially children are at risk for impaired neurological development upon chronic exposure [2]. It is estimated that nearly half a million of children in the United States have blood lead levels high enough to cause irreversible damage to their health, lead paint being the major source of lead toxicity in children [1].

Typically, lead-intoxicated patients present with neurological complaints and neurobehavioral disorders. However, toxic levels of lead do not only affect the nervous system but also hematopoiesis and renal function [2-5]. Lead-induced liver damage is an uncommon finding and has anecdotally been reported [6]. The resulting histopathological changes have rarely been described in humans. However, descriptive animal studies have been reported [4].

Clinical presentation

We describe the case of a 40-year-old man, an immigrant from Iran, who presented himself at the emergency department of our hospital with severe, constant, upper abdominal pain. His complaints had started a few weeks before presentation, following a short stay in Iran. However, over one day his pain had progressed. His medical history included exacerbating-remitting multiple sclerosis, for which he received weekly interferon-beta injections. Due to chronic pain he also used Iranian opium regularly. There was no history of alcohol abuse. Physical examination revealed a sweating, afebrile, hemodynamically stable, non-icteric patient in evident pain. Upon examination of the abdomen, bowel sounds were decreased and especially the right upper abdominal quadrant was tender to palpation. No involuntary guarding or abnormal abdominal masses were observed.

The initial differential diagnosis of the symptoms included biliary dyskinesia associated with the use of opium, chole(cysto)lithiasis, peptic ulcer disease, gastric perforation, nephrolithiasis, mesenterial ischemia and possibly porphyria. Laboratory findings included a normocytic anemia (hemoglobin 5.7 mmol/L; hematocrit 0.27, MCV 84 fl) and elevated liver function tests: AST 66 U/L (N 0-35), ALT 92 U/L (N 0-45), gamma-GT 729 U/L (N 0-40), without an acute-phase response. Renal function was normal. Ultrasonography and CT imaging of the abdomen did not

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demonstrate any pathological findings nor (subphrenic) free air. During upper digestive endoscopy no macroscopic abnormalities were observed, no hemobilia was seen. Gastric antral and corpus biopsy specimens showed moderate chronic focal active gastritis, negative for Helicobacter pylori. Additional laboratory findings included an elevated ferritin level, maximally 1024 μg/L, iron binding capacity of 39 μmol/L (N 45-90), iron concentration of 27 μmol/L (N 10-32), iron saturation of 68% (N 20-50), vitamin B_{12} of 667 pmol/L (N 150-700), folic acid of 20.3 nmol/L (N > 6.0), lactate dehydrogenase of 197 U/L (N 0-250) and haptoglobin of 1.0 g/L (N 0.3-2.0), thus excluding iron deficiency, hemolysis and vitamin B_{12} deficiency. Viral serology was negative for hepatitis B and C. No antinuclear antibodies (ANA), anti-smooth muscle antibodies, anti-mitochondrial antibodies or liver kidney microsome 1 (LKM 1) antibodies were detected, thus making auto-immune hepatitis unlikely. A peripheral blood smear showed basophilic stippling of erythrocytes (Fig. 1). This finding, in combination with the patients' clinical presentation and reported Iranian opium use, pointed towards lead intoxication [7]. Lead intoxication is also occasionally referred to as "painter's colic", due to the associated colic-like abdominal pain.

The serum lead concentration was strongly elevated at 860 μg/L (normal <0.3 mg/L). The zinc protoporphyrin/ heme ratio was maximally elevated at 1.25 mM/M (N 0.0 – 0.22), indicating disruption of heme production. Most probably the source of lead was the ingestion of lead-contaminated Iranian opium, recently reported to be contaminated with lead [7].

A liver biopsy that was taken ten days after hospital admission because of elevated liver function tests demonstrated extensive microvesicular and macrovesicular steatosis with a patchy, zonal distribution, together with portal and intralobular lymphocytic infiltrates and the presence of some lymphocytes in the epithelium of the bile ducts, consistent with lymphocytic cholangitis (Fig. 1). In the hepatocytes, bile intracytoplasmic pigmentation was present. The liver parenchyma showed a disrupted architecture with the presence of regeneration nodules and a few foci of minor pericellular fibrosis. In the Kupffer cells, iron was demonstrated by Perls staining.

Treatment consisted of chelating therapy with i.m. dimercaprol and i.v. edetate calcium disodium ($CaNa_2EDTA$) during five days, followed by oral chelating therapy consisting of succimer. For pain relief he received methadone. Opium use was discontinued. The patient was discharged from hospital in good clinical condition after 14 days. His pain had subsided and his hemoglobin level had slighty increased to 6.1 mmol/ L and the serum lead level had plummeted from 860 to 20 μg/L. His liver function tests had strongly improved. Figure 2 shows the course of the liver function tests during hospitalization.

The patient did not show up for visits scheduled at the outpatient clinic and was lost for follow-up. This meant a planned analysis for lead content of a sample of the patients' opium stock could not be conducted.

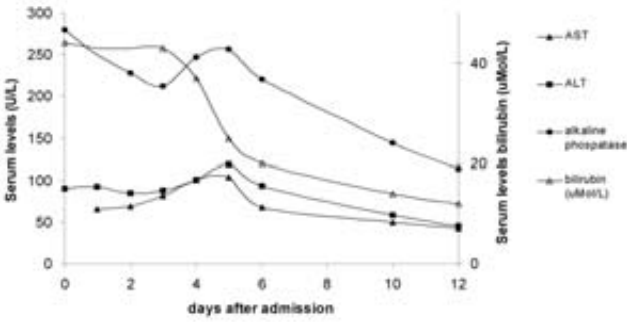

Fig 2. Evolution of the serum values of the liver enzymes and of bilirubin.

Discussion

Most case reports describe the chronic effects of lead intoxication affecting the nervous, hematopoietic and renal systems in mammals [1-5]. (Sub)acute intoxication is a rare event and has only been described as an unusual cause of hepatitis in a case report almost 30 years ago [6]. The four patients described in that case report were intoxicated after ingestion of lead and opium pills and presented with vomiting, abdominal/back pain, sweating, limb pain and headache. Liver biopsies showed a high lead content and a non specific hepatitis. A few animals studies are available as

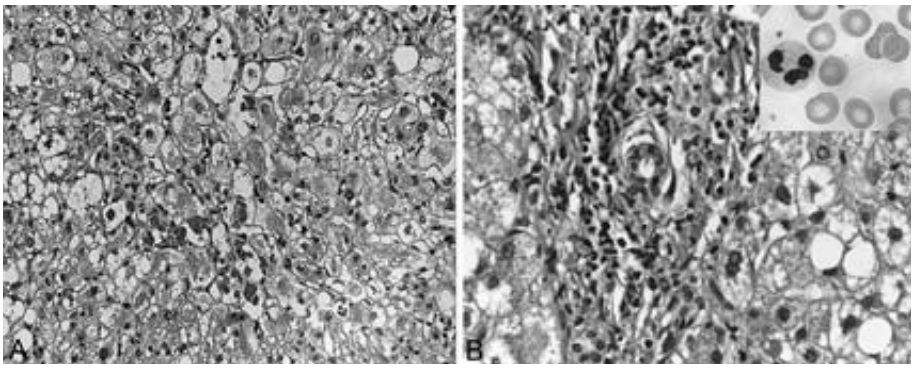

Fig 1. Macrovesicular steatosis and inflammation and activation of Kupfer cells (A) and lymphocytes in the epithelium of the bile ducts, consistent with lymphocytic cholangitis (B). Inset right corner: basophilic stippling of erythrocytes.

well [4, 8]. Subacute lead poisoning in geese and dogs caused Kupffer cell hemosiderosis, vacuolation of the cytoplasm of the hepatocytes, bile plugging with bile pigmentation and disorganization of the architectural structure. Liver cell necrosis was also described. The severity of the histological findings did not correlate with the hepatic lead concentration. These findings are in accordance with the changes in the morphology of the liver biopsy of our patient, although bile plugs were not found in our patient.

Lead exposure results in oxidative stress of the red blood cells and in haematological disturbances, reduced heme synthesis with consequent anaemia and increased variability in shape and size of the erythrocytes. The breakdown of erythrocytes results in increased deposition of iron in the reticulo-endoplasmatic system, demonstrated by the iron deposition in the liver Kupffer cells, as seen in our patient together with anemia. This resulted in the observed increase in serum values of ferritin and iron saturation together with a decrease in iron binding capacity, whereas the thrombocyte and leucocyte count were not affected in our patient. The breakdown of erythrocytes can be reversed by chelating therapy and anti-oxidation therapy by e.g. the administration of succimer [1, 9]. Although we hypothesized that the patient ingested lead-contaminated opium, it is unlikely that opiates contributed to the histopathological changes since adverse effects of opiates on the liver have never been reported [10]. No signs of sepsis were present in this patient which makes an infectious cause as a contributing factor to the cholestasis unlikely.

The course of the serum values of the liver enzymes in our patient suggests (partial) reversibility of the histological findings. Since the patient was lost for further follow-up, a control liver biopsy was not taken and a control lead level was not determined.

In **conclusion**, the differential diagnosis of severe abdominal pain associated with anemia should include lead intoxication, a condition that may be accompanied with hepatitis, cholangitis and hemosiderosis.

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