CASE REPORT

A rare cause of severe lactic acidosis

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SUMMARY

Sarcoidosis is a multisystem disease of unknown aetiology with a classic histology of non-caseating granulomas. It most often occurs in those below the age of 50 years, and has a female preponderance. The main targets, often symptomless, are the lung and hilar lymph nodes, although liver involvement is not uncommon. Hepatic sarcoidosis encompasses a broad spectrum of presentations, from asymptomatic hepatic granulomas with slight liver function test derangement to severe liver involvement with cholestasis, advanced liver cirrhosis or chronic liver failure. Mortality due to acute liver failure is far less common than lung and heart involvement. We describe a case of fulminant liver failure with multiorgan failure presenting initially with chronic non-specific symptoms, in addition to minimal abnormal investigations such as mild anaemia, neutrophil leucocytosis and mild obstructive liver dysfunction. Presenting features included confusion, hypotension, oliguria and rapidly deteriorating liver function with severe lactic acidosis. Postmortem examination confirmed extensive systemic sarcoidosis.

BACKGROUND

Though deranged liver function is not uncommon in acute medical patients, we believe sarcoidosis should be considered as a differential diagnoses in such patients.

Systemic sarcoidosis was not considered during our patient's illness. Postmortem examination, however, established extensive non-caseating granulomas of multiple organs including the liver, confirming extensive systemic sarcoidosis with marked hepatic involvement as the cause of death.

CASE PRESENTATION

A 45-year-old Caucasian woman presented to the accident and emergency (A&E) department following a witnessed collapse, with subsequent agitation and confusion. Her medical history consisted of multiple hospitalisations and visits to her general practitioner with vague symptoms such as myalgia, arthralgia and non-specific abdominal pains. Her comorbidities included controlled hypertension, stable angina, type 2 diabetes mellitus controlled with insulin and metformin 850 mg two times a day, polycystic ovary syndrome and obesity (body mass index of 34). She was also investigated for syncopal episodes, for which a REVEAL XT cardiac rhythm monitoring device was inserted. This was removed 2 months prior to admission as it did not demonstrate a cardiac cause of syncope.

The patient's family history was unremarkable. She lived with her husband, never smoked and

consumed alcohol occasionally. She denied any recent travel abroad.

On examination in the A&E department, she was unkempt, confused and uncooperative, with a Glasgow Coma Scale (GCS) score of 12/15. She was mildly hypothermic with a temperature of 34.9°C, breathing unaided with a respiratory rate of 16/min. Her oxygen saturations were 98% on room air and she was bradycardic at a rate of 56 bpm. Blood pressure on admission was 96/55 mm Hg. Despite 2.5 L of initial crystalloid/normal saline fluid resuscitation, she remained hypotensive (92/40 mm Hg) and oliguric. The remainder of the general examination was unremarkable except for absent bowel sounds.

INVESTIGATIONS

Initial bed-side investigations demonstrated capillary blood glucose of 5.1 mmol/L, 2+ urinary protein on dip-stick testing and mixed acidosis on arterial blood gases with elevated lactate (pH 7.24, PO₂ 12 kPa, PCO₂ 6.12 kPa, HCO₃ 16.7 mmol/L, base excess -11.5, lactate 12.3 mmol/L, chloride 99.4 mmol/L). The full blood count showed normocytic normochromic anaemia with haemoglobin of 82 g/L, predominantly neutrophil leucocytosis of 21.3×10⁹/L and raised C reactive protein of 144 mg/L. Her renal function demonstrated slightly raised urea of 11.3 mmol/L with normal creatinine of 75 mmol/L, mild hyponatraemia at 128 mmol/L and normal potassium at 3.8 mmol/L. Liver function tests (LFTs) revealed raised gamma-glutamyl transferase (GGT) at 240 u/L, alkaline phosphatase (ALP) at 287 u/L, normal alanine aminotransferase at 36 iu/L, normal bilirubin at 16 µmol/L and slightly low albumin at 33 g/L. Corrected calcium was marginally raised at 2.66 mmol/L. The patient's international normalised ratio (INR) was 1.3 and activated partial thromboplastin time ratio 1.3 at admission. Paracetamol and salicylate levels were undetectable. The initial ECG demonstrated sinus bradycardia with first degree heart block.

Previous investigations showed mildly deranged LFTs with normal calcium and normal liver on abdominal ultrasound.

DIFFERENTIAL DIAGNOSIS

1. Severe sepsis of unknown origin with encephalopathy and lactic acidosis
2. Severe biliary sepsis with lactic acidosis
3. Acute on chronic lactic acidosis due to chronic metformin treatment
4. Lactic acidosis caused by reduced peripheral perfusion and hepatic dysfunction due to poor gut perfusion.

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TREATMENT

In view of this patient's confusional state, hypothermia, raised lactate and marked neutrophil leucocytosis, the working diagnosis at this stage was sepsis of unknown origin with severe lactic acidosis due to septicaemia. She was started empirically on a broad spectrum antibiotic, piperillin-tazobactam, following blood cultures.

She became progressively agitated and uncooperative, hindering medical management, hence she was sedated and ventilated. Fluid optimisation continued using a Flowtrac cardiac output monitor (Edward Life Science).

Following fluid resuscitation with 2.5 L of crystalloid 0.9% sodium chloride, 1 L of gelatine based colloid, 400 mL of 20% albumin and 2 units of red cells, our patient demonstrated a marginal improvement of her metabolic acidosis. Her oliguric renal impairment, initially thought to be secondary to hypovolaemia, persisted.

She quickly became dependent on a combination of epinephrine and norepinephrine with the aim of achieving cardiovascular stability. The cardiac dysrhythmia that started as benign first degree heart block changed to a sinister Mobitz type 2 s degree heart block with a bradycardic rate of less than 30 bpm, warranting urgent transvenous pacing following a short period on transcutaneous pacing.

Subsequent to transvenous pacing, the patient's epinephrine requirement decreased transiently. A bedside transthoracic echocardiogram demonstrated good left ventricular function but a significantly dilated right ventricle with severe tricuspid regurgitation. This raised the suspicion of a pulmonary embolism as a possible cause of her cardiovascular instability, thus an urgent CT pulmonary angiogram (CTPA) along with a contrast CT of the abdomen and pelvis were carried out.

CTPA demonstrated pulmonary consolidation alongside non-occlusive pulmonary emboli in the right pulmonary artery. This raised the suspicion of pneumonia. However, the patient's oxygenation remained reasonable.

The CT scan of the abdomen and pelvis showed patchy liver perfusion with a suggestion of liver metastases, multiple loops of collapsed small bowel, a significant amount of free abdominal fluid and extensive inflammatory changes in the upper abdomen.

Given the non-resolution of the lactic acidosis and the suspicious intra-abdominal findings on the CT scan, an emergency laparotomy was performed, which demonstrated, in addition to significant peritoneal transudate free fluid, a coarse liver with questionable perfusion. No evidence of intestinal ischaemia was identified. A liver biopsy was not undertaken.

Owing to suspicious reduced hepatic perfusion and persistent lactic acidosis, alongside, an infusion of *N*-acetylcysteine infusion was administered to prevent further deterioration in hepatic function. Venovenous haemodiafiltration was initiated to treat lactic acidosis, assist fluid management and clear any endotoxins.

Despite fluid resuscitation and inotropic support, the patient's lactic acidemia persisted and she remained haemodynamically unstable, thus needing the addition of vasopressin, for which she rapidly reached the maximum recommended dose. The required spectrum of antimicrobial cover widened due to persistent neutrophil leucocytosis with a white cell count of $38.7 \times 10^9/L$; gentamicin at a dose of 3 mg/kg was therefore administered. Despite haemofiltration/haemodialysis, the aspired lactate clearance still could not be achieved and the blood lactate increased to over 20 mmol/L.

The coagulation state declined 6 days after presentation. The patient required further 1200 mL of fresh frozen plasma to correct the elevated INR of 1.8; while a further 2 units of

packed cells were administered to treat a postoperative drop in haemoglobin to 65 g/L. Though renal figures and the fluid status demonstrated marginal improvement on renal replacement therapy (urea 7.7 mmol/L, creatinine 125 mmol/L), oliguria persisted. Biochemical markers of her liver function did not improve; she developed an elevation of liver enzymes and worsening synthetic function.

OUTCOME AND FOLLOW-UP

Despite receiving epinephrine, norepinephrine and vasopressin along with ongoing fluid optimisation, cardiovascular stability could not be achieved. Regardless of mechanical hyperventilation, sodium bicarbonate infusion, high inspired oxygen concentration of 100% and renal replacement therapy, her lactic acidosis worsened to 26 mmol/L and subsequently to unrecordable levels. Following discussions with the family, a decision to withdraw active treatment was made, and she died immediately.

A postmortem examination revealed evidence of wide-spread lymphadenopathy with prominent mediastinal, upper abdominal and para-aortic lymph nodes. There were multiple creamy nodules in most organs including lymph nodes, heart, lung, liver, spleen, kidneys and bone marrow. The liver was replaced by glaucomatous inflammation composed of coalescing non-caseating granulomas with multinucleated giant cells, fibrinoid necrosis and a background of extensive fibrosis. A similar process was found in the spleen.

Microscopic examination demonstrated granulomatous inflammatory change negative for acid-fast bacilli (AFB). Evidence of sepsis in the chest, heart or abdomen was not found. Blood and body secretion cultures were all negative. Taking the AFB-negative inflammatory granulomas into consideration, a final diagnosis of extensive sarcoidosis leading to multiorgan failure and severe lactic acidosis was made. Marked neutrophil leucocytosis was attributed to sarcoid infiltration of the bone marrow.

DISCUSSION

Sarcoidosis is a systemic disorder of unknown aetiology characterised by non-caseating epithelioid granulomas disturbing normal tissue histology. The current hypothesis for the origin of sarcoidosis is an exposure to a yet unidentified antigen in genetically predisposed individuals.¹

Prevalence is estimated at 1–40 in 100 000; young people (commonly 20–40 years of age), particularly women, are mostly affected. The disorder is more common in northern Europe and the USA, being rare in Japan. In the USA, African-Americans have a threefold higher lifetime risk of developing sarcoidosis compared to the white population.^{1 2}

Sarcoidosis primarily affects lungs in 90% of patients and lymph nodes in 75%, with 66% having some form of associated liver involvement. Eyes (25%), skin (25%) and salivary glands are commonly affected. Isolated involvement of the spleen, heart and bone marrow are less common.^{2 3} Isolated hepatic sarcoidosis is extremely rare.

Diagnosis of systemic sarcoidosis is clinically challenging and is based on a compatible clinical history of two organ system involvement, supportive histological evidence of non-caseating granulomas and exclusion of other granulomatous diseases. The absence of occupational or domestic exposure to toxins is vital in the diagnosis of sarcoidosis, as is confirmation of the lack of drug-induced disease.^{3 4}

Five percent of patients with systemic sarcoidosis present with constitutional symptoms such as weight loss, night sweats and fever. A non-productive persistent cough and shortness of

breath suggest lung involvement.^{5 6} Although hepatic granulomatous involvement in sarcoidosis is common, it is interesting to note that, in most cases, patients are asymptomatic and derangement of LFTs is either mild or absent.^{7–9} This is concurred in our case report.

Abnormalities in LFTs are encountered in 20–40% of patients, yet clinical expression of hepatic disease is not common.⁹ Patients with hepatic sarcoidosis may have incidental findings of hepatosplenomegaly (15–40%) or lymphadenopathy (15%), or may rarely present with symptoms suggestive of complications such as cholestasis or Budd-Chiari syndrome.³ Specific liver signs such as jaundice, pruritus, ascites and hepatic encephalopathy are very rare unless the disease is advanced.¹⁰

Cirrhosis and portal hypertension are only reported in 1% of patients with sarcoidosis. Intrahepatic cholestasis, commonly reported in African-American patients, may clinically resemble primary biliary cirrhosis or sclerosing cholangitis. Sarcoidosis can also coexist within these two entities. Furthermore, extrahepatic biliary tract obstruction in sarcoidosis due to enlarged lymph nodes has also been described, but this was not the case in our patient.^{11–13}

The diagnosis depends on the investigations and diagnostic procedures undertaken. Depending on disease activity, hyperglobulinaemia, an increase in serum ALP, GGT and bilirubin alongside slightly elevated transaminase levels are the classic laboratory findings. An increase in ALP can be found in up to 90% of patients with signs and symptoms of hepatic disease, but in only 10% of cases with histological evidence.^{12 13} Serum ACE is elevated in 55% of cases, though not pathognomonic.³ Serial measurements help in monitoring disease activity and response to treatment. Hypercalcaemia occurs in 10–20% of patients and is due to overproduction of 1, 25-dihydroxycholecalciferol from activated macrophages. Elevated levels of Ca 19–9 in cholestasis are also encountered.^{6 7 13} Measurement of IgM and antimitochondrial antibody can be helpful in distinguishing primary biliary cirrhosis from hepatic sarcoidosis. A lack of antinuclear cytoplasmic antibody may allow exclusion of primary sclerosing cholangitis, alongside the absence of inflammatory bowel disease and lack of periductal fibrosis in histology.¹⁴

Granulomas may be visualised on CT as multiple discrete, low attenuation, non-enhancing nodules of varying sizes, usually 0.5–0.8 cm. As the granulomas increase in size, they become confluent and need to be differentiated from a variety of infective or neoplastic conditions (eg, liver metastases, lymphoma and angiosarcoma).¹⁵ In a reported autopsy case series, hepatic granulomas were demonstrated in 70% of patients with sarcoidosis, although it is interesting to note that liver biopsies only pick up 50–65% of these.^{16 17}

Treatment of symptomatic hepatic sarcoidosis or that affecting liver function consists of systemic glucocorticoids, with a consideration of liver transplant in the rare cases of liver cirrhosis. Other drugs reportedly being used include immunomodulators such as methotrexate and azathioprine. Symptomatic splenomegaly and portal hypertension are typically treated with splenectomy.¹⁴

A recently published case report describes a case of hepatic sarcoidosis, rapidly progressing to portal hypertension and cirrhosis. As well as deranged LFTs, the patient exhibited pancytopenia and left upper quadrant pain, hence a splenectomy was undertaken. Histopathological examination of the spleen revealed non-caseating granulomas and giant cells. Radiological evidence of liver cirrhosis was detected 6 months following diagnosis of hepatic sarcoidosis complicated by portal hypertension.¹⁴

Although that case is similar to ours, our patient unfortunately presented in the later stage; she was haemodynamically unstable and had severe lactic acidosis. The diagnosis of sarcoidosis was not considered, hence histological samples were not obtained until the postmortem.

Life-threatening complications of sarcoidosis are rare. The mortality rates were estimated to be 4.32/1 000 000 between 1988 and 2007. Respiratory and cardiac complications are the most common causes of death. The leading cause of death in such patients is as a result of pulmonary fibrosis followed by cardiac failure. Acute fulminant hepatic failure as a complication of sarcoidosis is rare, with an incidence of less than 5% in patients with hepatic sarcoidosis. Other fatal complications include renal and neurological involvement.¹⁸

Glycolysis in the cytoplasm produces the intermediate metabolite pyruvate. Under aerobic conditions, pyruvate is converted to acetyl CoA to enter the Krebs cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase to lactic acid. In aqueous solutions, lactic acid dissociates almost completely to lactate and H⁺.

The liver removes 70% of lactate. Uptake involves a monocarboxylate transporter and the less efficient process of diffusion (important at concentration >2 mmol/L⁻¹). Within the periportal hepatocytes, metabolism involves the processes of gluconeogenesis and, to a lesser extent, oxidation to CO₂ and water. Mitochondria-rich tissues such as skeletal and cardiac myocytes, and proximal tubule cells, remove the rest of the lactate by converting it to pyruvate. Less than 5% of lactate is renally excreted. Blood lactate concentrations reflect the balance between lactate production and clearance. Impaired lactate clearance, rather than hypoxic tissue production of lactate, is the cause of hyperlactaemia in stable septic patients, and in patients with renal and hepatic failure.¹⁹

Lactic acidosis is a rare but serious metabolic condition, with a mortality rate of 50%. It classically causes a high anion gap metabolic acidosis and is divided into two types. Type A lactic acidosis is most common and is caused by tissue hypoperfusion or severe hypoxaemia, while type B is associated with underlying haematological malignancies, drugs such as antidiabetic and antiretroviral therapy, chronic alcohol intoxication and inborn errors of metabolism. The commonest causes encountered in the emergency department are postictal phase, alcohol intoxication and severe sepsis.²⁰

Lactic acidosis associated with deranged liver function should also raise the suspicion of malignancy, in particular, lymphoma. A liver biopsy should be promptly undertaken to aid early diagnosis and improve prognosis, as well as exclude other potential diagnoses.²¹

One of the first biguanides, phenformin, was linked with elevated lactate, hence withdrawn from the US market in 1976. Metformin is now the most widely used biguanide. The UK Prospective Diabetes Study (UKPDS) provided evidence of decreased long-term complications with metformin in obese diabetic patients. There is speculation, however, that metformin may also cause lactic acidosis, theoretically by inhibiting gluconeogenesis and impairing mitochondrial activity.^{22 23}

A major Cochrane meta-analysis recently failed to demonstrate a statistically significant increase in the risk of developing elevated lactate with metformin in comparison to non-metformin treatment.¹⁹ However, metformin has been found to be associated with lactic acidosis in patients with other pathophysiological conditions that can reduce lactate clearance such as congestive heart failure, renal failure, hepatic dysfunction, septicemia, decreased tissue perfusion and hypoxia. The overall

incidence of metformin-induced lactic acidosis (lactate >5 mmol/L) is 5/100 000 patients, according to the Food and Drug Administration (FDA). Almost all reported cases occurred in patients who have had risk factors for lactic acidosis.^{22 24–26}

Neither metformin, lactate nor creatinine levels predict outcome of lactic acidosis in metformin use. Patients with previously normal renal function and younger patients with no other comorbidities may develop metformin-induced lactic acidosis.²⁷ We do not believe our patient's lactic acidosis was caused iatrogenically by metformin, although this indeed could have been a contributing factor to its accumulation.

This case study highlights the importance of considering systemic sarcoidosis as a differential diagnosis in patients presenting to A&E or acute medical unit with vague symptoms, particularly if LFTs are deranged.

Learning points

- ▶ Sarcoidosis is a systemic disorder of unknown aetiology characterised by non-caseating epithelioid granulomas.
- ▶ Sarcoidosis must be considered in patients who present with abnormalities of two or more systems, particularly in the case of mildly deranged liver function tests with no clear cause.
- ▶ Hepatic granulomas are common in sarcoidosis, but liver biopsies only detect up to 65% of these.
- ▶ Metformin-induced lactic acidosis must be considered, particularly in patients with organ failure.
- ▶ Mortality due to sarcoidosis is rare, but results mainly from cardiac and pulmonary involvement.

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