CASE REPORT

Case Report: Isolated hepatosplenic sarcoidosis treatment improving glycaemic control in a type 1 diabetic patient [version 1; peer review: 1 approved]

Sérgio Pina, Teresa Salero, Mariana Figueiras, Rui Osório, Sofia Amálio
Serviço de Medicina Interna, Hospital de Faro, Faro, 8000-386, Portugal

Abstract
Sarcoidosis is a multi-systemic disease characterized by non-caseating granulomas in various organs. The aetiology is still unknown. Although the liver is the third most commonly affected organ, hepatosplenic sarcoidosis without lung involvement is very uncommon. There is a high frequency of certain autoimmune illnesses observed in sarcoidosis, but association with type 1 diabetes is infrequent. We present the case of a 31-year-old woman, with type 1 diabetes mellitus diagnosed 22 years before with a glycated haemoglobin (HbA1c) above 14%, diabetic nephropathy, retinopathy and neuropathy, hypercholesterolemia and beta thalassemia. She was medicated with an angiotensin-converting enzyme inhibitor, a dihydropyridine calcium antagonist and insulin. The patient presented with a 4-month history of tiredness, abdominal pain, weight loss and hepatosplenomegaly. Abdominal ultrasound revealed hepatomegaly with regular contours, diffuse heterogeneous texture, containing numerous nodules with slight enlargement of the spleen. Serum angiotensin converting enzyme (ACE) was 67 IU/L and a sedimentation rate of 120 mm/h. Computer tomography (CT) scan confirmed hepatosplenomegaly and suggested infiltration in both organs. Liver biopsies were compatible with sarcoidosis. After ruling other organ involvement, a diagnosis of isolated hepatosplenic sarcoidosis was provided and prednisolone (40mg/day) was started. After a few months the patient developed a corticoid-induced myopathy confirmed with electromyography. Prednisolone was reduced to 20mg/day and azathioprine (50mg/day) treatment initiated. After a 7-month treatment, chest-abdomen-pelvis CT scan showed a marked reduction of the nodularity and hepatosplenomegaly and after 1 year the patient was completely asymptomatic (HbA1c, 7.5%; ACE, 24IU/L). At 18-month follow-up there was no evidence of recurrence (HbA1c, 7%), with optimum glycaemic control with total daily insulin dose lowered to half. This is an uncommon case in which the treatment of hepatosplenic sarcoidosis with regression of sarcoid tissue can help explain the improvement of glycaemic control in this patient.
Keywords
Hepatic sarcoidosis, Esplenic sarcoidosis, Type 1 Diabetes, Hepatosplenomegaly

Corresponding author: Sérgio Pina (s.menezespina@gmail.com)

Author roles: Pina S: Conceptualization, Formal Analysis, Writing – Original Draft Preparation, Writing – Review & Editing; Salero T: Writing – Review & Editing; Figueiras M: Writing – Review & Editing; Osório R: Writing – Review & Editing; Amálio S: Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2020 Pina S et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.


Introduction
Sarcoidosis is a chronic multi-system pathology characterized by epithelioid granulomas without caseation or necrosis. The highest incidence occurs between individuals aged between 25 and 40 years old and the reported prevalence varies from 20 cases per 100000 in the UK to 64 cases per 100000 in Scandinavian and African-American populations. Sarcoidosis is more frequent in women, with lung and mediastinal lymph node involvement in 90% of cases. Although the liver is the third most commonly affected organ, hepatosplenic sarcoidosis without lung involvement is very uncommon. Coexistence of sarcoidosis and immune-mediated diseases has been described in a previous case series and an association between diabetes and sarcoidosis was found, but this is rarely reported.

We report an uncommon case of glycaemic control in a type 1 diabetic after successful isolated hepatosplenic sarcoidosis treatment with immunosuppressant treatment.

Case presentation
A 31-year-old woman, with type 1 diabetes mellitus, diagnosed 22 years before, hypercholesterolemia and beta thalassemia. The patient had history of a poor metabolic control with glycated haemoglobin (HbA1c) above 14% (normal range 4–5.6%), diabetic nephropathy, retinopathy and neuropathy and arterial hypertension. She was medicated with 10 mg ramipril per day, 5 mg amlodipine per day, insulin detemir 26 IU in the morning and 20 IU at night, as well as prandial aspart insulin determined by pre-meal glucose level, meal size and content. The patient was allergic to glargine insulin.

The patient presented at a diabetology consult in July 2016 with a 4-month history of tiredness, anorexia, abdominal pain and weight loss (8% of total weight). At physical examination she was found to have hepatosplenomegaly. The smooth, regular liver edge was felt 4 cm below the right costal margin for a total span of 14 cm. An urgent abdominal ultrasound was performed revealing hepatomegaly with regular contours, diffuse heterogeneous texture, containing numerous hyperechogenic, nodular, confluent, mostly infracentimetric images, the largest reaching about 17 mm in diameter. The spleen was slightly enlarged with no other significant alterations.

On August 2016, the patient was admitted to the Internal Medicine ward, Hospital de Faro, for further investigation. On admittance, the patient presented no other alterations at physical exam, besides those described above related to the abdomen.

Blood tests were performed, including blood count and blood cultures, electrolytes, hepatic viruses, autoantibodies, C3 and C4 complement levels, immunoglobulins, serum protein electrophoresis, sedimentation rate and serology for multiple granulomatous diseases (results in Table 1). Laboratory results of note were elevated serum angiotensin converting enzyme (ACE) of 67 IU/L, a sedimentation rate of 120 mm/h, a gamma polyclonal peak in protein electrophoresis, a hepatitis C viral (HCV) titre of 90 IU/mL and doubtful HCV antibody reaction with negative viral load. Asymptomatic hypercalcaemia was also detected that was promptly corrected with isotonic saline hydration and 4mg of zoledronic acid intravenously over 15 min. Hypochromic microcytic anaemia was due to thalassaeemia history.

Further imaging studies were performed. Chest x-ray revealed no important changes (Figure 1), but chest-abdomen-pelvis computer tomography (CT) scan confirmed hepatosplenomegaly and revealed infiltration in both organs. No other alterations were found (Figure 2).

Bone marrow biopsy showed sideropenic bone marrow with reactive histological characteristics. To confirm the aetiology, liver biopsies were performed, which revealed granulomatous inflammation, non-caseating granulomas, with no necrosis, acid-fast bacilli, fungi or other organisms (Figure 3).

Based on the above findings, a diagnosis of sarcoidosis was strongly favoured, and a diagnosis of isolated hepatosplenic sarcoidosis was confirmed after ruling out skin, ganglionar and ophthalmic involvement.

The patient was discharged to outpatient consultation and medicated with prednisolone (40 mg per day) after testing negative for latent tuberculosis. Following a few months of treatment, she presented with fatigue, pelvic girdle muscle weakness and muscle pain. Corticosteroid-induced myopathy was diagnosed (later confirmed with electromyography) and prednisolone was reduced to 20 mg per day, and azathioprine was added (50 mg per day) for maintenance.

After 7 months of treatment, chest-abdomen-pelvis CT scan showed a marked reduction of the nodularity and hepatosplenomegaly (Figure 4). Other tests supported the new imaging results, such as reduction of sedimentation rate to 56 mm/h. Surprisingly, there was a progressive improvement of HbA1c to 9.5%. HCV serologies came back negative, suggesting cross reaction.

After one year of treatment, the patient was completely asymptomatic and insulin needs had diminished. HbA1c continued to drop to 7.5% and ACE was 24 IU/L. At 18-month follow-up there was no evidence of recurrence, HbA1c was 7%, with optimum glycaemic control with total daily insulin dose lowered to half.

Discussion
Sarcoidosis is a disease of unknown aetiology that can implicate almost any organ, but most commonly affects the lung, the lymph nodes, eye and skin. Involvement of the gastrointestinal tract is infrequent and hepatic sarcoidosis without lung disease is documented in only 13% of patients with systemic sarcoidosis. It can be very challenging to diagnose since liver and spleen involvement are usually asymptomatic and functional derangement is not common. If not totally asymptomatic, the clinical presentation of hepatosplenic sarcoidosis can be weakness, weight loss and hepatosplenomegaly. Our patient presented with non-specific systemic symptoms, such as poor glycaemic control, tiredness, anorexia, abdominal pain and enlargement of liver and spleen. The diagnosis was confirmed using CT scan imaging and liver biopsy.
### Table 1. Haematology and biochemical parameters of the patient at initial presentation (August 2016).

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>98 g/L</td>
<td>120-150 g/L</td>
</tr>
<tr>
<td>Mean Corpuscular Volume</td>
<td>65.3 fL</td>
<td>83-100 fL</td>
</tr>
<tr>
<td>Mean Corpuscular Haemoglobin</td>
<td>20.8 pg</td>
<td>27-32 pg</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>8.2×10⁹/L</td>
<td>4-10×10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>535×10⁹/L</td>
<td>150-400×10⁹/L</td>
</tr>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>131 mmol/L</td>
<td>136-144 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.9 mmol/L</td>
<td>3.3-5.1 mmol/L</td>
</tr>
<tr>
<td>Chlorine</td>
<td>102 mmol/L</td>
<td>101-111 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>14.8 mg/dL</td>
<td>8.4-10 mg/dL</td>
</tr>
<tr>
<td>Parathryoid Hormone</td>
<td>1pg/mL</td>
<td>&lt;68.3 pg/mL</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>13ng/mL</td>
<td>30-40ng/mL</td>
</tr>
<tr>
<td><strong>Thyroid function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid-stimulating Hormone</td>
<td>4.22 uIU/mL</td>
<td>0.35-4.94 uIU/mL</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>0.93 ng/dL</td>
<td>0.52-3.88 uIU/mL</td>
</tr>
<tr>
<td><strong>Hepatic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>80 IU/L</td>
<td>40-150 IU/L</td>
</tr>
<tr>
<td>Gama Glutamy-transpeptidase</td>
<td>298 IU/L</td>
<td>9-36 IU/L</td>
</tr>
<tr>
<td>Aspartate Transaminase</td>
<td>20 IU/L</td>
<td>5-34 IU/L</td>
</tr>
<tr>
<td>Alanine Transaminase</td>
<td>45 IU/L</td>
<td>&lt;55 IU/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.4 mg/dL</td>
<td>0.2-120 mg/dL</td>
</tr>
<tr>
<td><strong>Viral hepatitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Surface Antigen</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Surface Antibody</td>
<td>37 mIU/mL</td>
<td></td>
</tr>
</tbody>
</table>

**Serologies**

- Treponema pallidum: Negative
- Brucella: Negative
- Coxiella burnetii: Negative
- Epstein-barr virus: Negative
- Cytomegalovirus: Negative
- Toxoplasma gondii: Negative
- HIV: Negative

**Autoimmunity**

- Anti-glutamic acid decarboxylase: Positive
- Anti-mitochondrial Antibody: Negative
- Anti-smooth muscle Antibodies: Negative
- Anti-liver-kidney microsomal Antibody: Negative
- Anti-phospholipid Antibodies: Negative
- Antinuclear Antibody: Negative
- Anti-neutrophil cytoplasmatic: Negative

**Protein electrophoresis**

- Albumin: 3.07 g/dL, 3-6 g/dL
- Alpha 1: 0.43 g/dL, 0.06-0.26g/dL
- Alpha 2: 1.38 g/dL, 0.47-1.05g/dL
- Beta: 1.22 g/dL, 0.48-1.07g/dL
- Gamma: 1.79 g/dL, 0.51-1.31g/dL

**Others**

- Sedimentation rate: 120 mm/h
- Angiotensin-converting enzyme: 43 IU/L, 12-68IU/L

![Thorax x-ray](image_url)

**Figure 1. Thorax x-ray of the patient showing normal pathology at initial presentation (August 2016).**
Figure 2. Chest-abdomen-pelvis CT scan revealing hepatosplenomegaly at initial presentation (August 2016).

Figure 3. Liver biopsy showing granulomatous inflammation and non-caseating granuloma at initial presentation (August 2016).

Figure 4. Chest-abdomen-pelvis CT scan showing reduced hepatosplenomegaly 7 months after treatment.
Sarcoidosis dysregulates vitamin D production, increasing extrarenal production by macrophages in granulomas resulting in elevated levels of 1,25-dihydroxyvitamin D₃, that can help explain the asymptomatic hypercalcemia in this case.

The liver plays a central role in the control of glucose metabolism, especially in diabetic patients, by controlling various pathways, including glycogenesis, glycogenolysis, glycolysis, gluconeogenesis and helping with insulin sensitivity⁶,⁹,¹⁰.

The regression of hepatic sarcoid tissue after immunosuppressant treatment restored some of the capacity of the patient’s liver to play its central role in glucose metabolism leading to a marked reduction in her insulin needs and in HbA1c with better metabolic control.

Consent
Written informed consent was obtained from the patient for the publication of the report and any associated images.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

References

Wilbert S Aronow  
Department of Cardiology, New York Medical College at Westchester Medical Center, Valhalla, NY, USA

This is an excellent case report which shows that treatment of hepatosplenic sarcoidosis with regression of sarcoid tissue can improve glycemic control in a diabetic treated with insulin.

Coexistence of sarcoidosis and immune-mediated diseases has been described in a previous case series and an association between diabetes and sarcoidosis was found, but this is rarely reported.

Is the background of the case's history and progression described in sufficient detail?  
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?  
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?  
Yes

Is the case presented with sufficient detail to be useful for other practitioners?  
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** cardiovascular disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com