Cirrhosis and partial portal thrombosis leading to severe variceal bleeding, an unusual presentation of sarcoidosis

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Cirrhosis and partial portal thrombosis leading to severe variceal bleeding, an unusual presentation of sarcoidosis.

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ABSTRACT

Introduction: Sarcoidosis is a systemic granulomatous disease, characterized by the formation of non-necrotizing granulomas. Even though granulomas are frequently found in liver biopsy, related symptoms rarely occur. In the current article, a case report is pictured to increase the knowledge on portal hypertension in hepatic sarcoidosis.

Clinical situation: A 62-year-old female was diagnosed with variceal bleeding for which elastic banding was performed. The patient was admitted to the intensive

Met opmerkingen [MM1]: p. 1, l. 11: disease, characterized...

Met opmerkingen [MM2]: p. 1, l. 17: the intensive care...

care unit (ICU) as the bleeding persisted and she evolved in hemorrhagic shock. Liver ultrasound detected nodular hepatomegaly and partial portal thrombosis. Chest CT showed diffuse hilar adenopathies and interstitial micronodular lesion. Finally, PET-CT detected metabolic active liver, bone marrow, and upper and lower diaphragmatic adenopathies.

Clinical resolution: Multidisciplinary discussion brought major advantages in rapid diagnosis and prompt effective treatment. Cirrhosis was diagnosed by liver nodularity on imaging and liver biopsy. Sarcoidosis diagnosis was supported by the biopsies of liver and lymph node, which yielded non-caseating granulomas infiltration. Chest CT scan and PET-CT were also consistent with this diagnosis. The complementary analysis excluded differential diagnosis. The patient was treated with high-dose methylprednisolone with notable clinical improvements and discharge from the ICU.

Conclusion: Hepatic sarcoidosis can present as life-threatening bleeding due to variceal bleeding caused by portal hypertension. Differential diagnosis is broad when hepatic sarcoidosis is suspected. Therefore, a multidisciplinary discussion is warranted. Anatomopathological examination of two potentially involved organs should be considered to make the appropriate diagnosis. Further studies are requested to investigate the pathophysiological mechanism of portal hypertension.

INTRODUCTION

Systemic sarcoidosis is a multisystem granulomatous disorder with a prevalence ranging between two and 60 per 100,000 people [1]. Although the lungs are the most frequently affected organ, extrapulmonary sarcoidosis occurs in 30–50% of patients [1, 2]. Anatomopathological studies found liver involvement in 50 to 80% of the examined patients diagnosed with sarcoidosis [2, 3]. It is estimated that only 10 to 30% presents with elevated liver enzymes, and especially alkaline phosphatase [2, 3]. Furthermore, less than 15-20% of them mention abdominal pain or have hepatomegaly or splenomegaly [1, 2]. Progressive hepatic sarcoidosis may result in portal hypertension, portal thrombosis, and eventually in variceal bleeding. Data on this topic is scarce and the pathophysiologic mechanism is poorly understood [4, 5]. Finally, approximately six to eight percent evolves in cirrhosis [2]. In the current article, we present the clinical case of a 62-year-old female with hepatic sarcoidosis, who presented with life-threatening variceal bleeding. This study aims to underline the need for a multidisciplinary approach in complicated cases and increase the knowledge on portal hypertension in hepatic sarcoidosis.

CASE DESCRIPTION

Clinical situation

A 62-year-old female presented to the emergency department with acute abdominal pain and hematemesis. She mentioned progressive fatigue and weight loss for several months. The patient had a medical history of type two diabetes mellitus for

which she was treated with oral antidiabetic drugs. She denied alcohol and paracetamol consumption.

Physical examination revealed an apyretic patient (36.6°C tympanic), with an arterial blood pressure of 117/71mmHg and a regular heartbeat of 119bpm. The patient was not icteric. Abdominal examination revealed hepato-splenomegaly with a painless abdomen. Blood analysis showed an increased urea of 123mg/dL (normal range: 21-43mg/dL) and creatinine of 1.11mg/dL (normal range: 0.51-0.95mg/dL) with an estimated glomerular filtration rate of 53ml/min (normal values <60ml/min), a hyperkaliemia of 5.4mmol/L (normal range: 3.4-4.5mmol/L), and a hyperlactatemia of 6.5mmol/L (normal range: 0.7-2.1mmol/L). Increased liver tests were observed (aspartate and alanine transferase within the normal range, alkaline phosphatase of 993U/L (normal range: 35-104U/L), gamma glutamyl-transferase of 421U/L (normal values <40U/L), and total bilirubin of 1.24 mg/dL (normal range: 0-1.2mg/dL) with direct bilirubin of 0.8mg/dl (normal range: 0-0.3mg/dL)). Profound microcytic anemia with hemoglobin of 6.4g/dL (normal range: 11.7-15.1g/dL) was found. Gastroscopy detected esophageal varices grade II with active bleeding. No clear varices were found within the stomach, but blood clots were visualized on the fundus. Elastic banding was performed. The patient was initially treated with somatostatin, ceftriaxone (2g qd for seven days), and a transfusion of two blood units. The patient was admitted to the intensive care unit (ICU) for hemodynamic monitoring.

Initial workup with ultrasound detected splenomegaly, nodular hepatomegaly, and partial portal vein thrombosis (figure 1). Laboratory exams ruled out frequent causes of cirrhosis: viral hepatitis (hepatitis B and C), hemochromatosis, alfa-1

Met opmerkingen [MM3]: p. 4, l. 4: mmHg

Met opmerkingen [MM4]: 2. On p. 4 and 6, normal lab values should be indicated

Met opmerkingen [MM5]: 6. p. 4: also dL should be with capital L

Met opmerkingen [MM6]: l. 10: alkaline

Met opmerkingen [MM7]: l. 19 and 24: portal vein thrombosis

antitrypsin deficiency, Wilson disease. Anti-neutrophil cytoplasmic antibodies (ANCA), anti-mitochondrial antibodies (AMA) and anti-nuclear antibodies (ANA) were negative. Complementary PET-CT was performed to rule out malignancy in a patient with b-symptoms, hepato-splenomegaly, and partial portal vein thrombosis. This exam detected an impressive metabolic active liver, bone marrow, and upper and lower diaphragmatic adenopathies. The spleen showed no metabolic activity on PET-CT (figure 2). Additional high-rate chest CT scan found diffuse hilar adenopathies and bilateral interstitial micronodular lung lesions.

The bleeding persisted for two consecutive days with melena and hematochezia. Three other blood units and two units of fresh frozen plasma were transfused. Eventually, the patient became hemodynamically unstable with need for high dose norepinephrine, and somatostatin was switched to terlipressin. Tracheal intubation was performed preemptively to protect the airways due to the high risk of massive hematemesis with eventual aspiration.

Clinical resolution

A multidisciplinary discussion was organized to improve the rapidity and accuracy of the diagnostic procedure. The hematologist advised adenopathy and bone marrow biopsy. This excluded lymphoproliferative malignancies (normal karyotype, myelogram, absence of BCL1-2 translocation and monoclonal Ig peak), and found profound erythropoiesis reactive to severe anemia. The systemic disease specialist requested liver biopsy, magnetic resonance cholangiopancreatography (MRCP), autoimmune and microbiological assessment. Interferon-gamma release assays resulted indeterminate. Serology for Brucella, Coxiella Q, and Syphilis were

Met opmerkingen [MM8]: l. 21: cytoplasmic antibodies, anti-mitochondrial antibodies; anti-nuclear antibodies

Met opmerkingen [MM9]: p. 5, l. 13: The hematologist

Met opmerkingen [MM10]: l. 16: The systemic...

negative. Autoimmune hepatitis panel was negative, complement factors were not depleted, protein electrophoresis and immunoglobulins were normal. MRCP found nodular appearance of liver parenchyma without macroscopic bile duct abnormalities. Hence, it was not suggestive for primary sclerosing cholangitis. The diagnostic hypothesis of systemic sarcoidosis was put forward as angiotensin-converting enzyme was elevated (62U/L), and both chest CT and PET-CT had suggestive findings.

Another gastroscopy was ordered to evaluate if the gastric banding was successful. Ulcers with active bleeding, which was due to bleeds from the banded tissue, and limited gastric portal hypertension were found during this procedure. Therefore, the gastroenterologist placed a hemostatic stent, type SX-ELLA Stent Danis® 30x25x30 x 135mm, on the cardia. The device mechanically compressed the varices and controlled the hemorrhagic source. The stent could be removed seven days later. Prophylactic therapy with beta-blockers was commenced.

Adenectomy was performed by surgical removal of a lymph node in the left inguinal region. Anatomopathological examination of the lymph node revealed numerous naked tightly packed granulomas with some multinucleated giant cells without any necrosis nor acute inflammation (figure 3b). Gram, Giemsa, periodic acid Schiff, Grocott, Steiner, and Ziehl-Neelsen stains could not identify any microorganism. An associated lymphoma was also excluded. The liver biopsy showed also a similar strong granulomatous reaction evenly distributed in the parenchyma (figure 3a). The granulomatous reaction was accompanied by severe fibrosis. Considering the liver nodularity observed by ultrasound and PET-CT and the liver biopsy results, which found major architectural distortion of the liver, high

Met opmerkingen [MM11]: L. 22: bile duct

Met opmerkingen [MM12]: 4. p. 6: hemostatic stent on the cardia: unclear. Was this a Sengstaken tube to mechanically stop bleeding?

Met opmerkingen [MM13]: 3. p. 6, adenectomy: was this removal of a lymph node? Which region?

Met opmerkingen [MM14]: 1. On p. 2 and 6 the authors mention that the diagnosis of cirrhosis is confirmed by fibroscan. However, cirrhosis a histological diagnosis. The HE srain of the liver biopsy (Fig 3) shows an nodular liver with bridging fibrosis, a fibrous tissue stain could even better show this. The liver stiffness measurement by fibroscan is compatible with advanced fibrosis (F4), but the stiffness can also be influenced by other factors such as inflammation.

grade of fibrosis, and regenerative nodules, the diagnosis of cirrhosis was confirmed. Furthermore, the diagnosis of systemic sarcoidosis was made considering the pulmonary imaging, the typical histology, and the exclusion of other granulomatous diseases. The patient was hence treated with a high dose of methylprednisolone 1mg/kg/day for ten days. This was tapered afterward. Notable clinical improvements in performance scale were observed. After treatment, a control of the liver doppler ultrasound found no portal vein thrombosis. Moreover, lung function tests, which initially showed moderate restrictive disease with decreased diffusing capacity for carbon monoxide, evolved to a less restrictive pattern.

Met opmerkingen [MM15]: Was the thrombosis confirmed by power doppler or other imaging e.g. MRI, CT? Absence of color can be seen when the flow direction is perpendicular to the direction to the transducer.
REPLY: we did not perform any angio-CT or angio-MRI. The portal vein partial thrombosis was not observed by control doppler ultrasound.

Met opmerkingen [MM16]: 7. Were there any lung function tests performed, e.g. diffusion capacity?

DISCUSSION

Asymptomatic liver involvement is common in systemic sarcoidosis. However, evolution to portal hypertension and cirrhosis is rare but should not be overlooked as it can lead to life-threatening symptoms. Literature on this topic is scarce and based on case reports and series. A clinical case is hence described to increase the knowledge in this field.

The initial differential diagnoses of the current patient were broad. A multidisciplinary approach to a such complex patient was fundamental. Thanks to the combined expertise of the hematologist, internist, intensivist, and gastroenterologist, a rapid and accurate diagnosis was made. Specific and correct treatment was begun, which was crucial to control the life-threatening bleeding.

Histological changes even if typical are never specific. Therefore, a biopsy is usually optional when sarcoidosis has a classical presentation [6]. However, in an atypical presentation, as in our patient with hepatic involvement, biopsies of two potentially involved sites were helpful, by showing the typical sarcoid "naked" granulomas, excluding other etiology and by confirming the liver fibrosis. Indeed, different other granulomatous diseases may share similar clinical and pathological features [2, 3]. The combination of the pulmonary images, the elevated ACE with typical histology confirmed the final diagnosis of sarcoidosis.

It has been hypothesized that several mechanisms may increase intrahepatic resistances and could lead to portal hypertension. Maddrey *et al.* hypothesized that primary vascular injury drives to portal hypertension and sequentially to cirrhosis without affection of the bile ducts [4]. Arterial-venous shunts within hepatic granulomas may increase the portal blood flow. Modification and/or destruction of hepatic sinusoids due to granulomas may augment hepatic flow resistances. Moreover, thrombosis of portal and hepatic veins may cause respectively hepatic ischemia and congestion, with the rise of blood flow resistances [3, 4]. However, there is disagreement on whether hepatic sarcoidosis might cause progressive destruction of the bile ducts, through the portal and periportal granulomas, and might evolve in biliary cirrhosis [5]. Considering this last speculation, the presence of suppurative bile duct destruction could help to differentiate between sarcoidosis and primary biliary cholangitis (PBC). However, in our opinion, it would still be arduous to differentiate between the two. Further studies are needed to better understand the mechanism causing portal hypertension in sarcoidosis.

Whatever the pathophysiology may be, early detection of portal hypertension should be investigated in hepatic sarcoidosis before it could evolve in cirrhosis [5].

Conclusion

Hepatic sarcoidosis can have a life-threatening presentation as a hemorrhagic shock due to variceal bleeding. When this diagnosis is suspected a multidisciplinary discussion should be organized as a large amount of alternative diagnoses are possible. Anatomopathological examination of two potentially involved sites should be considered to make the appropriate diagnosis. This can lead to a rapid diagnosis and prompt appropriate treatment. Further studies are needed to understand how hepatic sarcoidosis can lead to portal hypertension.

DECLARATION

Ethics approval and consent to participate

The study was conducted following the Declaration of Helsinki and applicable regulatory requirements. The involved patient has given her consent to participate in the current study.

Competing interests

All authors declare that they have no competing interests with the content published in this manuscript.

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FIGURES

Figure legend

Figure.1 Portal vein partial thrombosis; right image: ultrasound color doppler, epigastric view, showing no flow in the portal vein, the thrombosis is underlined with white arrow; left side ultrasound: ultrasound spectral doppler, epigastric view, showing residual flow in portal vein; these images are taken on the same occasion and are consistent with portal vein partial thrombosis.

Met opmerkingen [MM17]: 5. Fig 1: In the legend, the left side image is mentioned twice. What kind of sections are presented? Subcostal images, Are the images taken at the same occasion or is there a time lapse? Does the arrow point to the thrombus which does not show color by color doppler? Was the thrombosis confirmed by power doppler or other imaging e.g. MRI, CT? Absence of color can be seen when the flow direction is perpendicular to the direction to the transducer.

Figure.2 Metabolic active adenopathies and liver with hepatomegaly; PET-CT sagittal image; metabolic active hepatomegaly is underlined with yellow arrow; metabolic active adenopathies are circled with white rings; not-metabolic active splenomegaly is underlined with a blue arrow.

Met opmerkingen [MM18]: Fig. 2: adenopathies

Figure.3 Liver and lymph node biopsies; 3a liver biopsy hematoxylin-eosin staining, on the left light microscope low magnification, on the right light

microscope high magnification; 3b lymph node biopsy hematoxylin-eosin staining, on the left light microscope low magnification, on the right light microscope high magnification; all the pictures show infiltration with sarcoid naked granulomas with some multinucleated giant cells and without any necrosis.