Introduction

Spontaneous hepatic haemorrhage (SHH), occurring in the absence of an external cause such as trauma or anticoagulant therapy, is a rare poorly understood and potentially lethal (mortality rate of up to 75% depending on the underlying cause and clinical status) surgical emergency due to liver capsular rupture with massive intra-abdominal haemorrhage, accounting for only 1% of admissions to specialist liver units.\textsuperscript{1,3,5} Although more commonly associated with the rupture of an underlying hypervascular hepatic tumour, there is a wide range of other even more rare underlying conditions, such as the Haemolysis, Elevated liver enzymes, Low platelet count (HELLP) syndrome in pregnant women, coagulation disturbances such as bleeding diathesis, connective tissue diseases, infections (in developing

Abstract

To report a clinical case of spontaneous hepatic haemorrhage with hemoperitoneum with no defined underlying cause. A detailed analysis and description of the spectrum of ultrasonographic (US), tomodensitometric (TDM) and angiographic findings - important diagnostic tools in this clinical setting – are done, in line with a review of the state of the art literature.

A 52-year-old woman with a poorly defined and inconclusive past medical history of gallstones and an autoimmune disorder treated with Salazopyrin complained of acute abdominal pain and vomiting. She was hospitalized with an initial diagnosis of acute pancreatitis. On the 6th day of hospitalization, US and TDM studies were done due to progressing abdominal pain with analytic worsening and new-onset of haemodynamic instability, although haemoglobin levels were normal. Liver haemorrhage with a large subcapsular haematoma, active parenchymal bleeding foci and hemoperitoneum was found. Initial and emergent surgical management with perihepatic packing was done. Due to active bleeding and haemodynamic instability nonresponsive to medical resuscitation, right hepatic artery angiography and embolization was performed the following day. A second laparotomy due to haemodynamic unresponsiveness, with "en bloc" evacuation of the hematoma and hepatic devitalized sequestrum, and haemostasis of the identified bleeding foci was performed two days afterwards. The patient eventually died from hemorrhagic shock.

Keywords

Spontaneous hepatic haemorrhage; Ultrasonographic findings of hepatic haemorrhage; Tomographic findings of hepatic haemorrhage; Management of spontaneous hepatic haemorrhage.

Resumo

É apresentado um caso clínico de hemorragia hepática espontânea com hemoperitoneu sem causa subjacente definida. É feita uma análise detalhada com descrição do espectro de achados ecográficos, tomodensitométricos e angiográficos – ferramentas diagnósticas importantes neste contexto clínico – em consonância com uma revisão da literatura.

Doente do sexo feminino de 52 anos - com história de litíase vesicular e antecedentes mal definidos e inconclusivos de patologia autoimune tratada com Salazopirina – que é avaliada por um quadro agudo de dor abdominal e vômitos, e hospitalizada com um diagnóstico inicial de pancreatite aguda. No 6º dia de internamento foi efetuada avaliação imagiológica com ecografia e tomografia computorizada por dor abdominal progressiva com agravamento analítico e instabilidade hemodinâmica “de novo”, apesar dos níveis normais de hemoglobina, tendo sido demonstrados sinais de hemorragia hepática com hematomas subcapsulares, focos de hemorragia parenquimatosa ativa e hemoperitoneu. Neste contexto, avançou-se para terapêutica cirúrgica em emergência com “packing” perihepático, seguida, no dia seguinte, de estudo angiográfico com embolização da artéria hepática direita, por instabilidade hemodinâmica e hemorragia ativa não responsivas ao tratamento médico. Pelo menos motivo, uma segunda laparotomia foi efetuada dois dias depois, com evacuação “em bloco” do hematoma e de sequestros hepáticos desvitalizados, e hemostase dos focos hemorrágicos identificados. Apesar das medidas efetuadas, o quadro clínico culminou em morte por choque hemorrágico.

Palavras-chave

Hemorragia hepática espontânea; Achados ecográficos de hemorragia hepática; Achados tomodensitométricos de hemorragia hepática; Terapêutica da hemorragia hepática espontânea.
countries) and miscellaneous causes. An association with cirrhosis, without an associated primary malignancy is also found in the literature.

Given the fact that most patients with SHH show unspecific symptoms (such as right upper quadrant or diffuse abdominal pain) and signs (malaise, nausea or hypotension), imaging – mainly dynamic multidetector computerized tomography (MDCT) – plays an important role in diagnosis and management, detecting and characterizing signs of hepatic haemorrhage with or without active bleeding, extension (intra-capsular vs intraperitoneal) and possible underlying causes.

Therapeutic management is complex, multidisciplinary and controversial, depending on the clinical status, the source and extent of bleeding. Intrapерitoneal bleeding with haemodynamically instability requires immediate surgery or selective embolization of the hepatic arteries to achieve haemostasis. Herein, a case-report of SHH is presented.

**Clinical Case**

A 52-year old female patient, with gallstones and an inconclusive past medical history of an undefined autoimmune disease (presumably, scleroderma) went to the Emergency Room with abdominal pain and vomiting that lasted for 5 days. She was under clinical investigation for skin thickening and hardening of the extremities below the knees and elbows associated with puritus – more prominent at the inferior extremities – with plaque-type morphea round cutaneous lesions with episodes of surrounding ring erythema; with associated muscle atrophy; without evident sclerodactyly; and associated beak-shaped nose. Pulmonary function was not determined and thoracic x-ray was normal. Renal and hepatic function tests were within the normal range. A suspicion of scleroderma with diffuse and severe skin involvement was set and treatment with Salazopyrin was started one year before the current clinical situation. A cutaneous biopsy was taken, with inconclusive results. Auto-antibodies (Rheumatoid factor, Anti-nuclear antibody including Anti-Jo1 and Anti-SCL 70 and Anti-neutrophil cytoplasmic antibodies) were negative. The patient subsequently refused biopsies (of the liver and skin), which revealed concave irregular edges and a reduced volume (best appreciated in image 4); - Some millimetric intraparenchymal foci of active bleeding seen as foci of high density accumulation similar to adjacent vessels after contrast administration - best seen at the arterial phase - mainly in the right hepatic lobe (curved arrows in images 5 and 6); - Ill-defined confluent parenchymal central areas of low density/low parenchymal enhancement suggesting areas of necrosis.

At initial clinical evaluation, the patient was normotensive (124/70 mmHg) with normal heart rate (87 bpm) and 97% of oxygen saturation; with a body temperature of 37°C; and had a firm and tender abdomen on the right quadrants, without signs suggesting peritoneal irritation. Analytic study revealed haemoglobin of 15 g/dL; leucocytosis of 18.4000 leucocytes with relative neutrophilia of 85,6%; bilirubinaemia of 5,10 mg/dL with predomination of direct bilirubin measuring 2,54 mg/dL; high levels of lactate dehydrogenase (LDH) of 365 U/L (1,7 x N), aspartate and alanine aminotransferases (TGO and TGP) of 432 and 568 U/L (16 x N) and pancreatic amylase and lipase enzymes of 1097 and 1241 U/L (20 x N); high levels of reactive C protein (RCP) of 2 mg/dL; normal levels of platelets around 399 x 10E3/µL; hypoalbuminemia (of 1,5 g/dL) and high levels of creatinine (2 mg/dL). The patient was hospitalized with the diagnosis of lactic acid pancreatitis – supportive care with aggressive hydration with isotonic crystalloid solution and food break was done, with clear liquid diet starting 48 hours after. Metoclopramide was given on a SOS regime.

After six days of hospitalization, due to persisting and progressing symptoms namely abdominal pain with the new onset of peritoneal irritation signs and haemodynamic instability (hypotension of 85-90/60-55 mmHg and tachycardia of 100-120 bpm) - and worsening analytic parameters, further radiologic investigation was performed. At his point, there was normalization of pancreatic amylase levels, with: persisting leucocytosis of 15.000 leucocytes with neutrophilia and high RCP levels of 5 mg/dL; worsening hepatic parameters with 1989, 1177 and 665 U/L (9,44 and 19 x N) of LDH, ASP and ALP levels; reduction of haemoglobin (9 g/dL), erythrocytes and haematocrit (of 27%), and a reduction of platelets (50 x 10E3/µL). International normalized ratio (INR) and prothrombin ratio (PR) were in the normal range of 1,2 and 73%.

Abdominal ultrasound, although limited by bowel gas, showed an enlarged liver (with a right hepatic lobe measuring 16 cm) with a diffusely altered heterogeneous parenchymal echostructure; signs of peritoneal hematic fluid seen as echogenic and heterogeneous peritoneal fluid; without other relevant signs, namely, splenomegaly, nor portal ectasia. Dynamic MDCT was performed for further evaluation, with image acquisition before and after IV contrast administration at the arterial (at 35 seconds after contrast administration), venous (70 seconds) and delayed phase (3 minutes) of enhancement, depicting:

- A large subcapsular hepatic hematoma surrounding both lobes, seen as a perihepatic heterogeneous fluid collection with areas of spontaneously high (45 UH) density from recent bleeding (solid arrow in image 2) – showing a “haematocrit effect” with fluid-fluid levels of different densities due to blood content of different ages (arrows in images 3 and 4); compressing the adjacent parenchyma, which revealed concave irregular edges and a reduced volume (best appreciated in image 4);

- Ill-defined confluent parenchymal central areas of low density/low parenchymal enhancement suggesting areas of necrosis.
necrosis/ischemia, mainly in the left hepatic lobe (curved arrow in images 3 and 4);
- Patent filiform arteries and a normal diameter patent portal;
- A small amount of hemoperitoneum, depicted as spontaneously dense (30-40UH) content deposited in Douglas space and surrounding the liver, from capsular hepatic rupture (solid arrows in image 1 and 2; also seen in images 5 and 6).

Two units of packed red blood cells and two units of platelets were transfused, with rising of haemoglobin levels to 10 g/dL and platelets to 134 10E3/µL. One hour after US and MDCT the patient remained with tachycardia (140-150 bpm) and arterial pressures of 85-95/55-65 mmHg. Due to hemodynamic instability, the presence of an extensive haematoma and signs of active parenchymal bleeding and hemoperitoneum, explorative laparotomy was first performed, the unique therapeutic available approach at that moment. Hemoperitoneum of large volume and hepatic haematoma with multiple capsular rupture sites were found. Peritoneal wash and perihepatic packing were done. Evacuation of subcapsular hematoma and hepatic resection were not performed in order to avoid severe haemorrhage.
Arterial embolization was unavailable in the Emergency Room at that moment.

The morning after (12 hours after surgery), hepatic artery embolization was attempted. Selective catheterization of the celiac trunk (image 7) and supra-selectivation of the right and left hepatic arteries (image 8) with a Progreat 2.7F catheter revealed focal irregularity in the proximal portion of the right hepatic artery (black arrow in images 7-8), with minimal contrast extravasation. Due to these findings and to limited therapeutic available options, right hepatic artery embolization was performed proximally with three microcoils of 0.018 inch. The post-embolization arteriogram (image 9) showed successful and complete embolization of this branch (white arrow). The procedure was performed without immediate complications.

Due to persistent haemodynamic instability, a second laparotomy was done (36 hours after the first surgical approach). Direct liver exploration was done after peritoneal wash, with signs of active bleeding – through the right anterior sectorial pedicle presumably from a portal branch source. “En bloc” evacuation of the hematoma and hepatic devitalized sequestrum and haemostasis of the haemorrhagic identified focus – using a suture and Surgicel stopper - were performed. Other multiple superficial haemorrhagic foci were controlled with cauterization. After the placement of Tachosil plates and new perihepatic packing, apparent haemorrhagic control was achieved. The patient subsequently deteriorated during the following day and died from uncontrolled bleeding.

Discussion

Spontaneous hepatic haemorrhage (SHH) is a surgical emergency with an unclear and probable multifactorial pathogenesis, related to a wide range of conditions that share a common feature of parenchymal and vasculature integrity impairment.\(^1\) An underlying hypervascular liver tumour (such as hepatocellular carcinoma, adenoma, metastases, haemangioma, focal nodular hyperplasia and other less frequent tumours such as angiomylipoma and angiosarcoma) is the most frequent cause.\(^4,5,10\) Other less frequent reported miscellaneous causes are coagulation disturbances such as bleeding diathesis (as seen in hepatic failure or thrombocytopenia) – that may precipitate or maintain bleeding;\(^1\) vascular lesions (i.e. peliosis hepatis); inflammatory/infectious processes with microaneurysm formation; nodular regenerative hyperplasia; amyloidosis; connective tissue disorders/autoimmune disorders (best described in patients with systemic lupus erythematous, polyarteritis nodosa or myositis); and cirrhosis without an associated with an underlying hepatocellular carcinoma - from macronodular cirrhosis and venous/lymphatic ectasias; with few case reports in the literature.\(^1,4,5,12\) SHH with rupture is also a known complication of some cases of pre-eclampsia and eclampsia in pregnancy, associated with the Haemolysis, Elevated liver enzymes, Low platelet count (HELLP) syndrome.\(^4\)
In the setting of autoimmune disorders, it is believed that a possible underlying pathologic mechanism is an impaired integrity with a weakened tissue that is vulnerable to a trivial or physiological event. Additionally, connective tissue or autoimmune disorders can be associated - concomitantly or serially - with a previous liver dysfunction, that can appear as a manifestation of the underlying disease or can reflect a primary liver disease with a common immunological pathogenic background. Diagnosis is made by serological, clinical and finally histological characteristics after exclusion of other potential causes.

The acute thrombocytopenia found in this case was hypothesized to be from accelerated destruction and/or multifactorial, presumably with an immune background – immune thrombocytopenia (ITP) and/or drug-induced immune thrombocytopenia (DITP); to an infectious cause due to the coexistence of neutrophilia; or related to thrombotic thrombocytopenic purpura (TTP), which could justify the liver involvement.

The pathological mechanisms of SHH are complex, poorly understood and accepted to be multifactorial. Hepatic necrosis can coexist if there is severe liver involvement (best described in cases of HELLP syndrome) - being vasospasm, endothelial damage, microvascular thrombi with disseminated intravascular coagulation (DIC) and hypoperfusion hypothesized mechanisms that cause necrosis and rupture. Parenchymal compression by a large subcapsular hematoma can also be the cause of parenchymal necrosis. Subcapsular bleeding and hematoma usually precedes hepatic rupture, with insidious vague local or systemic symptoms followed by an acute phase of increasing pain and collapse. In this specific case, an autoimmune undiagnosed disorder or a bleeding diathesis could be hypothesized as possible causes for bleeding. Bleeding diathesis from acute hepatic failure was excluded with normal values of PT and INR and thrombocytopenia was not sufficiently severe for this massive bleeding.

Due to its high mortality from intraabdominal massive haemorrhage and shock, and to the unspecific clinical manifestations (i.e. abdominal pain, nausea, vomiting and malaise and rarely shock) – imaging and laboratory evaluation play an important role in early diagnosis. Ultrasonography (US) and dynamic multidetector computerized tomography (MDCT) are the main diagnostic tools, and angiography is useful when there is also a therapeutic goal. Dynamic MDCT is the technique of choice due to its high accuracy, rapid acquisition and availability. It allows diagnosis, extension evaluation, location of foci of active bleeding and/or the determination of a possible underlying cause (i.e. tumour), detecting flow rates as low as 0.3 mL/min. In some cases, an underlying cause may not be detected by cross-sectional imaging – due to diffuse parenchymal involvement or to massive haemorrhage obscuring focal parenchymal alterations.

Management is complex and should be individualized - mainly to clinical stability, the underlying cause and extent of bleeding, hepatic function and/or the existence of hepatic fibrosis and coagulation status. Haemostasis is the primary goal of treatment, firstly done by active resuscitation with fluids, blood product replacement and correction of coagulopathy. Conservative management may be appropriate if the patient is stable and the liver capsule is intact, with few reports in the literature of stable patients with SHH associated with HELLP syndrome – with small and/or contained haematoma - who were managed conservatively with imaging monitoring of stability. An emergent and multidisciplinary treatment is needed with unstable patients or when there are radiological signs of active bleeding. Interventional radiology management with transarterial embolization of selected vessels or one of the main hepatic branches or even the hepatic artery – are the preferred ways to primarily achieve haemostasis if possible. MDCT allows guidance of angiography and embolization. Angiography identifies foci of active bleeding of at least 0.5-1 mL/min. Haemostasis is restored by decreasing perfusion pressure and promoting clot formation after embolization. The used embolic agent depends largely on individual medical experience and preference; and coils are definitive agents that can be used safely in hepatic embolization due to the dual hepatic blood supply and consequently low risk of clinical significant parenchymal infarction. Immediate exploratory surgery – usually with perihepatic packing in the first step with or without plication and/or hepatic artery selective or nonselective ligation - may be needed due to hemodynamic instability, after failure of conservative and radiological intervention treatments with persistent or recurrent bleeding and/or in the setting of massive hepatic bleeding/necrosis; or when embolization is not feasible. A planned re-laparotomy can be done with appropriate and individualized further management.

Hepatic resection is generally reserved for bleeding tumours in a second step and not to restore haemostasis after a carefully determination of staging and assessment of underlying liver function – was done successfully in selected cases on the acute phase in pregnant women and in patients with bleeding adenoma or HCC. Liver transplantation is an option when there is an uncontrolled haemorrhage or progressive fulminant liver failure. The management is even more complex if there is co-existing chronic liver disease, and those cases usually have poor outcomes. When haemostasis is achieved in the acute setting, subsequent treatment and outcome depend on the underlying condition.

Due to the difficulty to achieve diagnosis, this condition is associated with high mortality and strict therapeutic recommendations are lacking. Imaging and laboratory analysis play an important role in suspected cases. Outcome largely depends on the underlying pathology, extension and on the clinical background before the acute setting.

This rare condition with many underlying possible causes – in some cases obscure even after a careful clinical, imaging and pathological investigation – is a challenge in both diagnostic and therapeutic points of view, due to its rarity and complexity, incomplete understating and severity. Imaging plays a central role in the diagnosis and interventional radiology and surgery are cornerstones for management.

Acknowledgements

A special acknowledgement to Dr. Diogo Rocha, MD and Radiologist of Interventional Radiology of our Department, for his help in choosing the best images.
Received / Recebido 27/11/2017
Acceptance / Aceite 19/01/2018

Ethical disclosures / Divulgações Éticas
Conflicts of interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

References