## Case 48

A 75-year-old retired truck driver was referred for evaluation of abnormal liver function tests, which had been found at a routine check-up. He was asymptomatic. Prior medical history included a myocardial infarction 4 years before, benign prostatic hypertrophy, and jaundice at 17 years of age. He had never had a tattoo, drank very little, but had had blood transfusions following a prostatectomy in 2001. He had not recently travelled and was a non-smoker.

On examination, his pulse rate was 69bpm with frequent extrasystoles, and blood pressure was 145/80mmHg. He was apyrexial. There was no jaundice, pallor, lymphadenopathy, or oedema. Cardiovascular examination was unremarkable and his chest was clear. A liver edge was palpable 8cm below the costal margin, but percussion indicated a liver span of 15cm, which is only slightly enlarged. The spleen was clearly palpable, but did not cross the midline. There were no signs of chronic liver disease or portal hypertension.

### Investigations showed:

- Hb 13.4g/dL, WCC 7.66 x $10^9$/L, platelets 96 x $10^9$/L
- INR 1.2
- Bilirubin 22μmol/L ALT 78 IU/L, ALP 1269 IU/L, GGT 1017 IU/L, albumin 36g/L
- Blood film: platelets reduced on film. No platelet clumps seen. Howell–Jolly bodies seen.
- Ultrasound of the abdomen: the liver was diffusely heterogeneous and coarse in texture. The portal venous flows were normal. There was marked splenomegaly and the spleen had a bipolar length of 18cm. It, like the liver, had a very coarse, heterogeneous internal architecture.

### Questions

48a) Discuss the differential diagnosis in this patient.

48b) What are Howell–Jolly bodies and why are they significant?

48c) What further investigations would you plan?

48d) Discuss this condition.

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## Answers

48a) **What is the differential diagnosis in this patient?**

**Splenomegaly** may be caused by congestion, infiltration, immune activation or expansion of haematopoietic cell lines and reticuloendothelial cells within the organ. Clinical examination should include a search for chronic liver disease with portal hypertension (**congestive splenomegaly**), signs of haemolysis and anaemia (**extramedullary haematopoiesis** and expansion of reticuloendothelial cells), signs of chronic inflammatory disease or infections (**immune activation**), and signs of haematological **malignancy** (such as lymphoma or leukaemia) or any other **infiltrative** condition (such as amyloid). Hepatomegaly associated with splenomegaly may result from liver disease causing portal hypertension, extramedullary haematopoiesis, or infiltration by the same condition.

The presence of a high ALP with a raised GT suggests hepatic infiltration. Our patient had no signs of haemolysis and was not anaemic. There was no evidence of chronic liver disease or portal hypertension, nor was there any sign of a chronic inflammatory disorder.

**Malignant** infiltration is likely, most commonly a **lymphoma**. Even though the patient had no peripheral lymphadenopathy, axial lymph nodes may be present and would favour Hodgkin's disease. **Leukaemia** and **myeloproliferative** conditions may also enlarge liver and spleen. Primary **angiosarcoma** may originate in the spleen or metastasize from the liver to the spleen. Other **solid tumours** rarely metastasize to the spleen, but melanoma can (and does!). There was no evidence of previous or concurrent melanoma in or patient.

**Non-malignant** infiltration may result from extracellular depositions such as **amyloidosis**, **sarcoidosis**, or **tuberculosis** (associated with immune hyperplasia). Lipid **storage diseases** (e.g. Gaucher's disease) will not present at this age.

Our patient had a very, but not 'massively', enlarged spleen. Massive enlargement is defined as a spleen palpable >8cm below the costal margin. Some consider a spleen that crosses the midline as massively enlarged. Massive enlargement is caused by non-Hodgkin's lymphoma, chronic myeloid leukaemia, chronic lymphatic leukaemia, hairy cell leukaemia, myelofibrosis, and sarcoidosis.

48b) **What are Howell–Jolly bodies and why are they significant?**

Howell–Jolly bodies are remnants of the nucleus of red blood cells from their immature stages, which are then detected in mature erythrocytes on

a peripheral blood film. Such remnants are usually removed by the spleen, so the presence of Howell–Jolly bodies implies either absence of the spleen (e.g. splenectomy) or functional hyposplenism. Our patient clearly has a spleen that does not function. Diseases that are associated with impaired splenic function with an intact spleen include coeliac disease, sickle cell disease (splenic infarction), systemic lupus erythematosis, rheumatoid arthritis, Grave's disease, Sjögren's syndrome, chronic liver disease, alcoholism, inflammatory bowel disease, and Whipple's disease. Amyloidosis and sarcoidosis may also cause functional hyposplenism.

As a marker of hyposplenism, Howell–Jolly bodies are insensitive, but specific. They do not occur in mild hyposplenism. Their presence implies a level of functional hyposplenism thought to put the patient at risk of **overwhelming postsplenectomy infection**. Such infections are often cryptic with a short prodrome. Encapsulated organisms are usually responsible (*Streptococcus pneumoniae*, *Haemophylus influenzae*, or *Neisseria meningitidis*). Massive bacteraemia causes septic shock and disseminated intravascular coagulation. The mortality is up to 80% and death may occur within 24–48 hours.

48c) **What further investigation would you plan in this patient?**

A **CT scan** of the chest, abdomen, and pelvis would identify any lymphadenopathy in the chest or abdomen, a primary malignancy, or metastases. **Tissue** is needed to make a diagnosis. Because the liver is affected, a **liver biopsy** is appropriate, although a lymph node biopsy, bone marrow examination, or even a diagnostic splenectomy may be required.

**CT of chest and abdomen**: the liver has an expanded, rounded and heterogeneous appearance, measuring 14.5 x 10cm on axial section. The prostate is enlarged to 62mm diameter. There are degenerative changes of the spine. There is no suspicious bone lesion, and the lungs clear. The kidneys, adrenals, and pancreas are all normal. There is no gross lymphadenopathy, although there are some small mesenteric nodes and general streaking of the intra-abdominal fat (Fig. 48.1).

**Liver biopsy** shows **angiosarcoma** (Fig. 48.2 in central colour section).

48d) **Discuss this condition**

**Angiosarcoma** is a rare vascular tumour, accounting for 2% of all primary liver tumours. Primary angiosarcoma of the liver has a strong male predominance, with a 4:1 ratio of males to females. Individuals are usually > 60 years of age. Metastases to the lung, spleen and bones may occur

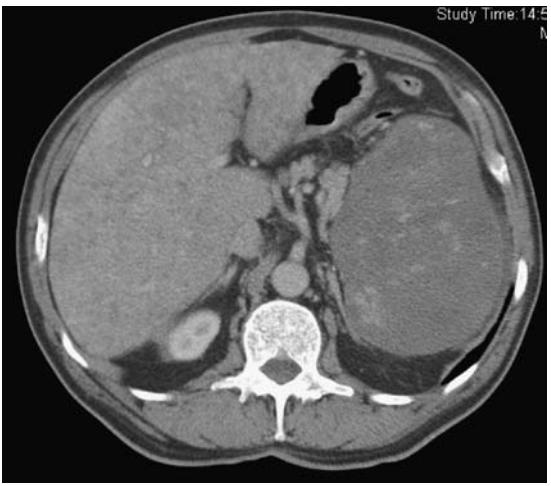


**Fig. 48.1** CT scan showing enlargement of liver and spleen, with a heterogenous parynchymal appearance in both organs.

in descending order of frequency. It is strongly associated with environmental or occupational exposure to carcinogens, including colloidal **thorium dioxide**, arsenic compounds, **polyvinyl chloride**, inorganic copper, radiation exposure, and anabolic steroids. A history of exposure is not commonly identified, however, as was the case with our patient. Nevertheless, because of the implications it is important that the patient is asked carefully about all their jobs and recreational activities.

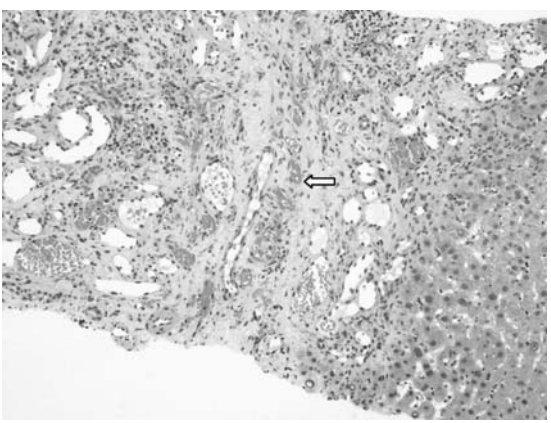

**Fig. 48.2** (see colour plate 26) Angiosarcoma of the liver. Vascular channels are identifiable (arrow), but not the characteristic spindle-shaped cells at this magnification.

An angiosarcoma shows areas of necrosis and haemorrhage with one of four different growth patterns: multiple nodules, a large dominant mass, a mixture of these, or (unusually) a diffuse infiltrating tumour, which was the case in our patient. Histopathology shows spindle-shaped cells, which may form vascular channels and are positive for vascular endothelial cell markers (CD31 and CD34) on immunohistochemistry (Fig. 48.2).

No effective therapy exists. Neither excision of a localized tumour nor chemotherapy alters the outcome. Cases of angiosarcoma diagnosed incidentally on liver transplantation for another indication show rapid recurrence and have a poor prognosis. Liver transplantation is therefore contraindicated. Survival from the time of diagnosis is <1 year in most instances, regardless of therapy. Management is palliative.

**Thorium dioxide** (Thorotrast, $Th^{232}$) was used worldwide as a radiographic contrast medium between 1928 and 1955, in a 25% colloidal solution. It is taken up by the reticuloendothelial cells. $Th^{232}$ is radioactive, emitting $\alpha$ and $\beta$ particles and $\gamma$ rays. It lingers in the body and may be seen on CT scan 50 years after administration. It can be responsible for hyposplenism, bone marrow failure, and is associated with angiosarcoma of the liver. Our patient had neither a history of Thorotrast administration, nor any sign of residual Thorotrast on CT imaging.

Exposure to **arsenic** comes from contamination of drinking water (India), burning of arsenic coal (China), or medicinal administration (Fowler's solution, used worldwide for chronic myeloid leukaemia 1931–1953). The polymerization of **vinyl chloride** in the polyvinyl chloride (PVC) industry since the mid 1930s lead to high levels of exposure among workers in the industry. The first case of angiosarcoma because of this occupational exposure was identified in 1974. Since then tight controls on the work environment have been implemented and cases caused by this exposure now occur rarely, if at all.

## Further reading

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Van Kampen RJW, Erdkamp FLG, Peters FPJ (2007). Thorium dioxide-related haemangiosarcoma of the liver. *Neth J Med*; **65**: 279–82.