A preterm infant with progressive abdominal distension

This report describes the case of a preterm infant with progressive liver enlargement causing abdominal distension at a few weeks of age. The liver biochemistry was normal with Doppler ultrasonographic evidence of increased vascularity within the liver parenchyma. The diagnosis was infantile multifocal hepatic haemangiomas. The clinical management required input from a multidisciplinary team. The spectrum of clinical presentation, diagnostic pathway and management options is reviewed.

Anju Singh[1]
MRCPCH, Consultant Neonatologist

Abigail Pugh[2]
MBBCh, Histopathology Specialist Registrar

Khalid Sharif[3]
FCPS, FRCS1, Consultant Hepatobiliary Surgeon

Girish Gupte[3]
MD (India), DNB, MRCP1, Consultant Hepatologist

[1] Neonatal Unit, Birmingham Women's NHS Foundation Trust
[2] Department of Histopathology, Birmingham Children's NHS Foundation Trust
[3] Liver Unit, Birmingham Children's NHS Foundation Trust

Keywords

hepatic haemangioma; propranolol; thyroxine

Key points

Singh A., Pugh A., Sharif K., Gupte G. A preterm infant with progressive abdominal distension. *Infant* 2014; 10(2): 65-68.

1. Multifocal hepatic haemangiomas can present with abdominal compartment syndrome.
2. Propranolol is the first line therapy for managing infantile haemangiomas.
3. Hypothyroidism is a recognised phenomenon associated with hepatic haemangiomas and therefore there is a need to regularly monitor thyroid function and treat appropriately.
4. A multidisciplinary approach is essential for managing a case of multifocal hepatic haemangioma.

A male infant was born at 29 weeks' gestation by an emergency caesarean section for maternal antepartum haemorrhage. His birth weight was 1,300g and head circumference was 28cm. There were no concerns during the antenatal period. His Apgar scores were 5, 8 and 8 at one, five and ten minutes. There was clinical and radiographic evidence of surfactant deficient lung disease. He received biphasic continuous positive airway pressure (CPAP) for one day followed by CPAP for another four days. In total he received 11 days of oxygen therapy. Enteral feeding with maternal expressed breast milk was introduced on day 3 of life and by day 7 the infant was on full feeds. His cranial ultrasound scans were normal.

Over the next six weeks the infant developed increasing abdominal distension with hepatomegaly. In week 7 of life, his abdominal girth increased by 0.5cm/day. Liver function tests were performed and were within normal limits. Abdominal ultrasound performed on day 43 showed an enlarged liver with coarse echotexture but no focal lesions or dilated ducts, and normal bidirectional venous flow. The gall bladder, spleen, kidney and adrenal glands were normal in size. The differential diagnosis at this point was either an oncological or storage disorder. Concurrently the baby developed tachypnoea and an oxygen requirement. There were no cutaneous lesions.

On the advice of the liver team, the following investigations were requested:

- Cortisol
- Triglycerides and cholesterol
- Fasting intermediary metabolites
- Lactate dehydrogenase
- Ferritin
- Thyroid function tests
- Alpha-1 antitrypsin
- Epstein-Barr virus
- Cytomegalovirus (hepatitis)
- Syphilis serology

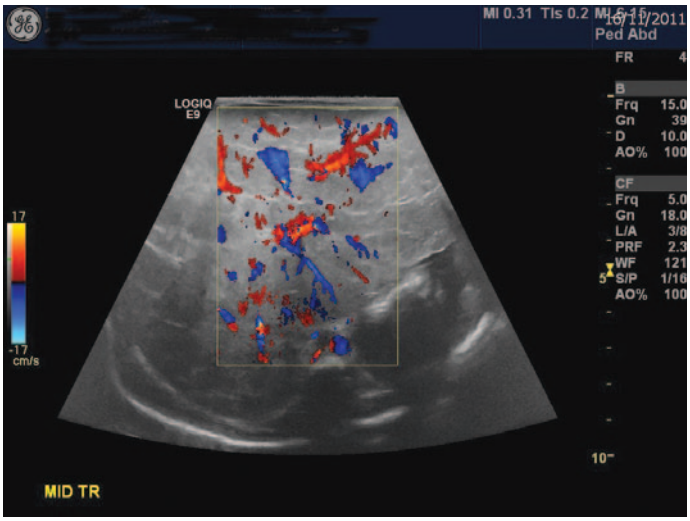

FIGURE 1 Doppler ultrasound of the liver showing increased vascularity.

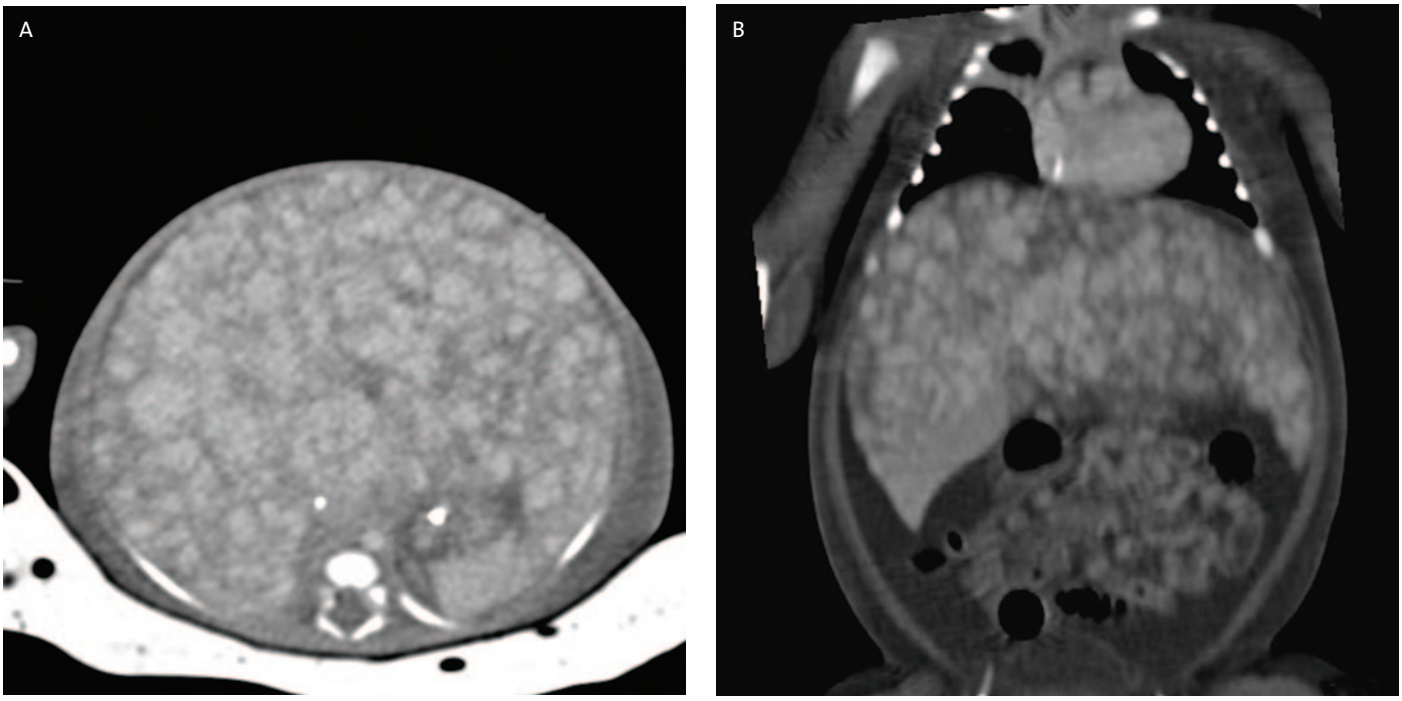

FIGURE 2 CT scans of the liver on day 48. A) Scan of the abdomen showing nodular deposits in the liver. B) A massively enlarged liver secondary to nodular deposits.

- Galactose 1 phosphate uridyl transferase (GALIPUT test for galactosaemia)
- Acylcarnitine analysis
- Urine analysis for catecholamine levels, organic acids, glycosaminoglycans (GAGs) and detection of reducing substances.

On day 47, the infant was transferred to the regional children's liver unit on nasal cannula oxygen. The next day his respiratory status deteriorated with increasing tachypnoea and respiratory acidosis. He was initially supported with CPAP and then conventional ventilation but following further deterioration the infant was switched to high frequency oscillatory ventilation. He was also hypotensive and was supported with an adrenaline infusion.

An echocardiogram was performed, which showed a structurally normal heart with a compressed inferior vena cava and normal contractility. The infant was screened for infection and started on broad spectrum antibiotics. Intravesical pressures, measured as a proxy for intra-abdominal pressures, were raised at 11-13mmHg[1]. Investigations revealed impaired clotting function, which was managed with plasma and cryoprecipitate. The platelet count was normal.

A repeat abdominal ultrasound scan showed the liver parenchyma to be heterogeneous and nodular – it appeared hypervascularised on colour Doppler ultrasound (**FIGURE 1**). A CT angiogram on day 48 (**FIGURE 2**) showed a massively enlarged liver secondary to diffuse nodular deposits, with some sparing of its inferior aspect. The main portal vein and artery were patent. There was marked ascites and consolidation of posterior aspects of both lungs.

At this point the differential diagnosis was a stage 4S neuroblastoma or a multifocal hepatic haemangioma. The infant was reviewed by the hepatic surgeons and the oncologists. Urinary tests for vanillylmandelic acid (VMA) and catecholamine levels were requested. Pending reports, in view of his clinical deterioration, he was given empirical chemotherapy with carboplatin and etoposide. Steroid therapy was also commenced. Since the results of the CT angiogram were inconclusive, the infant underwent an interventional radiology liver biopsy on day 50. The biopsy results were consistent with a hepatic vascular lesion (**FIGURE 3**). Immunohistochemistry showed strong endothelial staining for GLUT-1 (glucose transporter protein 1, **FIGURE 4**), which confirmed the diagnosis of hepatic haemangioma of infancy. The infant's ascitic fluid analysis showed a reactive effusion and the urinary catecholamine levels were not raised.

The empirical chemotherapy was stopped in view of the biopsy results and the infant was commenced on propranolol and diuretics. In order to reduce blood flow through the vascular lesion, on day 56 he underwent embolisation of the liver haemangioma via the segment 8 hepatic artery. This procedure was performed through a right femoral artery puncture. Following the procedure his ventilation improved and he was extubated to CPAP on day 58; on day 62 he was breathing air. At this time he was also noted to have an abnormally raised thyroid stimulating hormone (TSH) level of 75.6mU/L (normal value range = 0.4-3.5mU/L) and a free triiodothyronine (T3) level of 1.8pmol/L (normal value range = 3.6-8.5pmol/L). This is a known association with infantile haemangioma. The infant was started on 25µg oral thyroxine, once daily. There was no suggestion of Kasabach-Merritt syndrome as his platelet count was normal throughout the course of his illness. A repeat ultrasound scan, carried out on day 60 (**FIGURE 5**), showed that the liver remained enlarged and the parenchyma was heterogeneous. There were hypoechoic areas throughout the liver with some calcification. The liver was not as hypervascular as previously noted on scan. The steroids were gradually weaned and diuretics were stopped. His feeds were gradually increased and the infant was discharged on day 68 of life.

The child has been followed up at two to three-monthly intervals with clinical and ultrasonographic assessments. An endocrine review at 13 weeks of age found

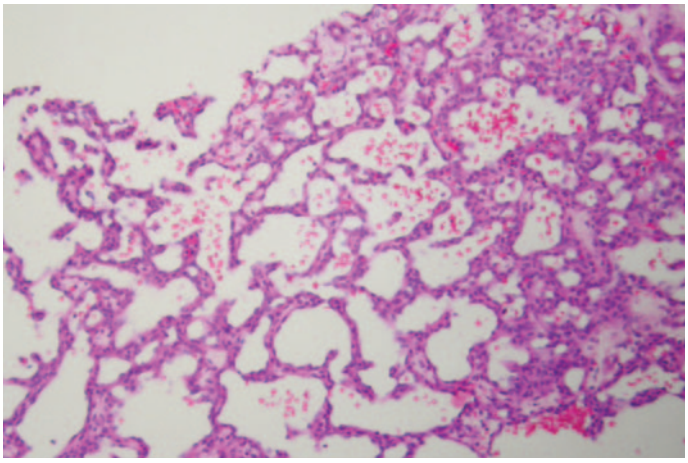

FIGURE 3 A histopathological section of the liver. The majority of the liver parenchyma has been replaced by anastomosing thin-walled vascular channels, lined by a single layer of flattened and low cuboidal endothelium with no cytologic atypia or hobnailing. There is minimal intervening stroma with a few entrapped hepatocytes.

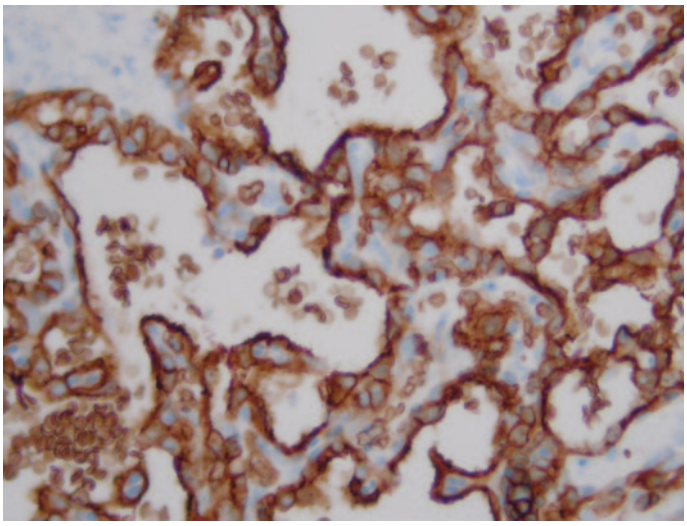

FIGURE 4 Immunohistochemistry of a liver section showing positive endothelial staining for GLUT-1.

him to be euthyroid. His thyroxine was stopped and repeat thyroid function tests, carried out four weeks later, were normal. At follow up at 15 weeks of age it was noticed that he had a small cutaneous haemangioma on the left buttock. Propranolol was stopped at 10 months of age. His most recent scan at 20 months of age, showed a heterogeneous liver with no hypervascularity or hypoechoic lesions. At this point he was thriving and developmentally appropriate. He is due to have a repeat scan in the autumn of 2014.

Discussion

The three main hepatic tumours seen in the perinatal period are haemangiomas, mesenchymal hamartomas and hepatoblastomas[2]. The clinical findings in neonates with hepatic tumours are less defined in comparison to those in older children. Neonates with focal hepatic haemangiomas have the best outcome. Abdominal compartment syndrome, due to the large hepatic mass and high output failure, can be seen in multifocal haemangiomas. These conditions can be life threatening[3-4]. Hypervascularity on Doppler ultrasound is suggestive of a haemangioma. Serial Doppler ultrasonography can provide guidance in progression of the vascular tumours.

Neuroblastomas are neural crest ectodermal tumours and are the most common solid tumors of infancy. Stage 4S neuroblastomas, seen exclusively in infants less than one year old, metastasize to the liver, skin and bone marrow and have a favourable prognosis. Fifty per cent of cases spontaneously resolve without requiring chemotherapy. In infants with progressive liver enlargement with secondary respiratory compromise and liver failure, the outcome may not be favourable. In 90-95% of cases, urine catecholamine levels are raised.

Hepatic haemangioma of infancy is a proliferative endothelial cell neoplasm involving the liver. GLUT-1 is a tissue specific marker that is co-expressed in infantile haemangiomas and placental microvasculature. The tumour has characteristic phases of rapid growth by proliferation of endothelial cells, lasting nine to 12 months and subsequent spontaneous involution in the next five to seven years. These lesions bear clinical and phenotypic similarity to infantile haemangiomas more commonly arising in the skin. They are not to be confused with epitheloid haemangioendotheliomas or adult hepatic haemangiomas. The former arise in adolescent or adult patients and have different histological appearances, are negative for GLUT-1 and have a malignant potential. Adult hepatic haemangiomas are, as their name suggests, seen in the adult population; they are vascular malformations that do not involute. Infantile hepatic haemangiomas are usually asymptomatic lesions detected incidentally on imaging. They are the most common tumours of the liver in infancy. Magnetic resonance imaging (MRI) is the investigation of choice in diagnosing hepatic mass in an infant[5-6]. Contrast enhanced CT or CT angiogram/MRI scan is the usual diagnostic pathway. Percutaneous biopsies can lead to uncontrolled haemorrhage.

Propranolol, a non-selective beta-blocker, is used as a first line therapy in infantile haemangiomas. It has been shown to be a safe and efficacious drug and possible explanations for its therapeutic effect include:

- vasoconstriction
- decreased expression of proangiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)
- an apoptosis trigger in endothelial cells.

There can be rebound growth after stopping propranolol therapy and the reported side effects of its use in infantile haemangiomas include hypotension, bradycardia, exacerbation of reactive airway disease, hypoglycaemia, diarrhoea, hyperkalaemia and drug interactions. The dose and duration of treatment with propranolol varies widely and many clinicians carry on treatment beyond the first year of life[7-13].

Other therapies used in the management of difficult haemangiomas are corticosteroids, interferon-alpha and vincristine. Embolisation should be considered early in infants presenting with cardiac failure secondary to shunting although the procedure may not have an effect on the underlying haemangioma. Resection is rarely required. Hepatic failure has been reported in infantile haemangioma, with the need for a liver transplant[14-15].

Hypothyroidism in infantile haemangiomas is a well reported phenomenon in the literature. High levels of type 3 iodothyronine deiodinase activity

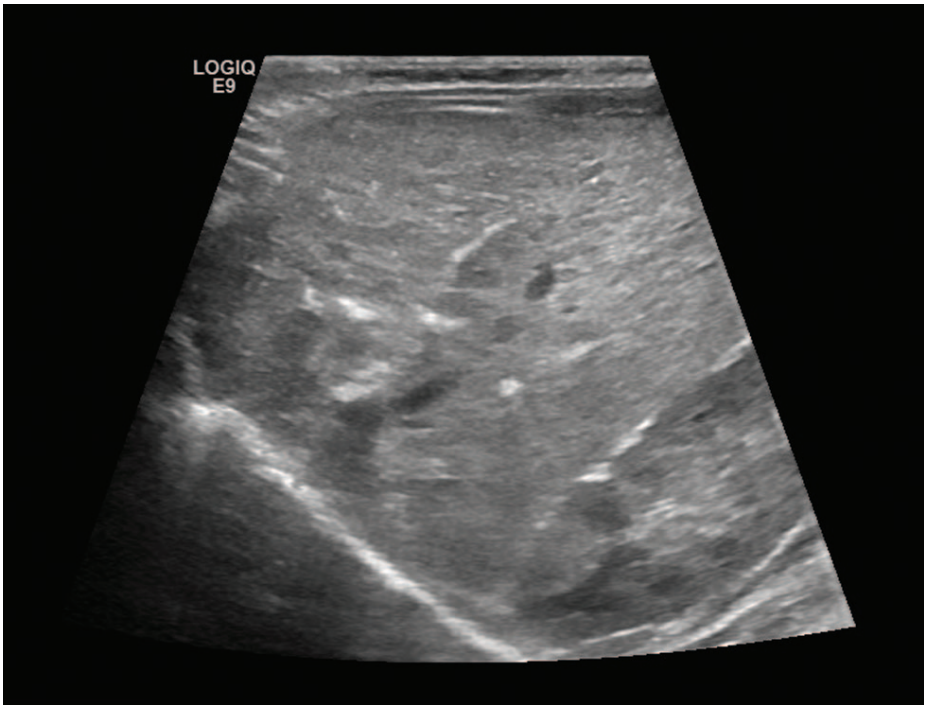

FIGURE 5 An ultrasound scan of the liver on day 60 showing an enlarged liver with heterogeneous parenchyma. There are subtle hypoechoic areas throughout the liver with some calcification.

have been identified in haemangioma tissue. This enzyme catalyses the conversion of thyroxine to reverse triiodothyronine and the conversion of triiodothyronine to 3, 3'-diiodothyronine, both of which are biologically inactive compounds. In the proliferative phase of haemangiomas, there is increased expression of angiogenic factors such as FGF. The expression of type 3 iodothyronine deiodinase in haemangiomas is probably due to induction of the enzyme by bFGF or other growth factors. Very high doses of levothyroxine may be needed in some infants with haemangiomas[16-17].

Conclusion

The case presented considers a preterm infant of 29 weeks' gestation who had an unremarkable initial course but developed increasing abdominal distension as a result of gross hepatomegaly. This is an unusual scenario in a neonatal unit but less so in a liver unit where the main differential diagnoses were either stage 4S neuroblastoma or a multifocal hepatic haemangioma. Referral to a specialist children's liver unit was instrumental in arriving at a timely diagnosis and achieving a good outcome for the infant.

Acknowledgement

The authors would like to thank Rohit Kumar (Specialist Registrar) and Alison Bedford Russell (Consultant Neonatologist) of the Neonatal Unit at Birmingham Women's NHS Foundation Trust for their valuable contributions.

References

1. **Kirkpatrick A.W., Roberts D.J., De Waele J. et al.** Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013;39:1190-206.
2. **Isaacs H. Jr.** Fetal and neonatal hepatic tumors. *J Pediatr Surg* 2007;42:1797-803.
3. **Schweinitz D.V.** Neonatal liver tumors. *Semin Neonatol* 2003;8:403-10.
4. **Maguiness S.M., Frieden I.J.** Management of difficult infantile haemangiomas. *Arch Dis Child* 2011:doi:10.1136/archdischild-2011-300851.
5. **Kassarjian A., Zurakowski D., Dubois J. et al.** Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. *Am J Roentgenol* 2004;182:785-95.
6. **Christison-Lagay E.R., Burrows P.E., Alomari A. et al.** Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg* 2007;42:62-67; discussion 67-68.
7. **Cuccaro P., Rapacciuolo A., Vitiello R. et al.** Propranolol for severe hemangioma of infancy. *J Cardiovasc Med (Hagerstown)* 2011;12:5.
8. **Zaher H., Rasheed H., Hegazy R.A. et al.** Oral propranolol: an effective, safe treatment for infantile hemangiomas. *Eur J Dermatol* 2011;21:558-63.
9. **Sarialioglu F., Erbay A., Demir S.** Response of infantile hepatic hemangioma to propranolol resistant to high-dose methylprednisolone and interferon-alpha therapy. *Pediatr Blood Cancer* 2010;55:1433-34.
10. **Sciveres M., Marrone G., Pipitone S. et al.** Successful first-line treatment with propranolol of multifocal infantile hepatic hemangioma with high-flow cardiac overload. *J Pediatr Gastroenterol Nutr* 2011;53:693-95.
11. **Abbott J., Parulekar M., Shahidullah H. et al.** Diarrhea associated with propranolol treatment for hemangioma of infancy (HOI). *Pediatr Dermatol* 2010;27:558.
12. **Holland K.E., Frieden I.J., Frommelt P.C. et al.** Hypoglycemia in children taking propranolol for the treatment of infantile hemangioma. *Arch Dermatol* 2010;146:775-78.
13. **Pavlakovic H., Kietz S., Lauerer P. et al.** Hyperkalemia complicating propranolol treatment of an infantile hemangioma. *Pediatrics* 2010;126: e1589-93.
14. **Zenzen W., Perez-Atayde A.R., Elisofon S.A. et al.** Hepatic failure in a rapidly involuting congenital hemangioma of the liver: failure of embolotherapy. *Pediatr Radiol* 2009;39:1118-23.
15. **Ferraz A.A., Sette M.J., Maia M. et al.** Liver transplant for the treatment of giant hepatic hemangioma. *Liver Transpl* 2004;10:1436-37.
16. **Huang S.A., Tu H.M., Harney J.W. et al.** Severe hypothyroidism caused by Type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000;343:185-89.
17. **Bessho K., Etani Y., Ichimori H. et al.** Increased type 3 iodothyronine deiodinase activity in a regrown hepatic hemangioma with consumptive hypothyroidism. *Eur J Pediatr* 2010;169:215-21.