Focal nodular hyperplasia of the liver: a link with sickle cell disease?

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Abstract
Focal nodular hyperplasia is a benign liver tumour that is rare in children. We report the second case of a child with sickle cell disease presenting with symptomatic focal nodular hyperplasia. The possible pathogenesis of focal nodular hyperplasia and the association with sickle cell disease are discussed.

Focal nodular hyperplasia of the liver is a rare benign lesion found predominantly in women during their reproductive years. It consists of a well circumscribed area of hyperplastic liver parenchyma that may contain a stellite fibrous scar. The lesion is usually asymptomatic and is an incidental finding. We describe a patient with sickle cell disease presenting with a symptomatic lesion of focal nodular hyperplasia. This is the second description of such an association and we discuss whether sickle cell disease is a pathogenetic mechanism for the development of focal nodular hyperplasia.

Case report
A 6 year old West Indian girl with homozygous SS sickle cell disease presented with abdominal pain, headache, and night sweats. She had been admitted one year previously with a chest infection and sickle crisis. She was taking prophylactic antibiotics. Apart from sickle cell disease there was no other significant medical or family history.

On examination she appeared anaemic but was not jaundiced. A firm non-tender mass was palpable in the epigastrum. The results of biochemical investigations were haemoglobin concentration 72 g/l, white cell count 8·1×10⁹/l, platelet count 213×10⁹/l, albumin 38 g/l, bilirubin 30 μmol/l, and activities of alkaline phosphatase 201 IU/l, aspartate transaminase 111 IU/l, and γ-glutamyltransferase 146 IU/l. A test for serum α fetoprotein was negative. An ultrasound scan showed a 6 cm well defined mass in the left lobe of the liver. The lesion had a similar density to normal liver on computed tomography (fig 1) and was shown to be avascular on hepatic angiography (fig 2).

At operation, after exchange transfusion, the solid mass was found to be restricted to segments 2 and 3 of the left lobe and was resected. She was discharged home on the ninth postoperative day.

The cut surface of the tumour was smooth with focal areas of haemorrhage, but there was no stellite scar. The microscopic appearance of fibrous bands transecting liver tissue with expanding portal tracts that contained dilated vascular channels and numerous bile ductules was typical of focal nodular hyperplasia (fig 3).

Discussion
Focal nodular hyperplasia is a rare benign liver tumour with fewer than 20% of cases presenting in children. The majority are asymptomatic and usually arise on the surface of the liver beneath the capsule. Their aetiology is unknown, although an association with oral contraceptives has been reported.

The radiological diagnosis depends on identification by ultrasound or computed tomography of a central scar. Angiographic findings of a hypervascular spoke wheel pattern of feeding vessels, such as we describe, have been reported. As their association with oral contraceptives has been reported, the lesion may arise in the liver due to their use.

The association with sickle cell disease is interesting. Several reports have been made of the association of sickle cell disease with benign liver masses of varied aetiology, including cysts, angiomas, and other forms of hyperplasia. Its cause is unclear but the majority of cases have been observed in black people. The possible association of sickle cell disease with the previously described case is uncertain, since it was diagnosed post mortem.

Focal nodular hyperplasia is a well described lesion in the liver. However, these cases suggest that it may be a more common lesion than previously thought, possibly as a result of the changing habits of the population.

Figure 1 Computed tomogram without contrast showing the mass in the left lobe of the liver (arrow).
Figure 3: Section showing regenerative nodules of liver parenchyma (thin arrow) transected by fibrous bands with expanded portal tracts (thick arrow) containing dilated vascular channels and bile ductules (magnification × 100).

vessels which produce a dense capillary blush are diagnostic but uncommon.5

The management of asymptomatic lesions should be to confirm the diagnosis of focal nodular hyperplasia by liver biopsy, excluding benign lesions such as hepatic adenoma, mesenchymal hamartoma, or haemangiomata and malignant lesions such as fibrolamellar carcinoma. Ultrasound follow up has been suggested. Symptoms may settle by withdrawal of oral contraceptives, but in other patients symptomatic lesions should be resected or if this is not possible they can be embolised.1

The pathogenesis of focal nodular hyperplasia has been considered to be neoplastic, hamartomatous, or a response to ischaemia or other focal injury. It has been suggested that the lesions arise as a hyperplastic response of liver parenchyma to differential blood flow caused by a pre-existing arterial malformation.6 Poorly perfused areas undergo atrophy and well-perfused areas develop regenerative nodules. Whelan et al suggested that increased blood flow and turbulence caused platelet disruption with thrombosis of smaller arterial vessels that lead to a release of platelet derived growth factor which may stimulate hepatocellular hyperplasia.7 Oral contraceptives may affect the hepatic vasculature and influence the development of focal nodular hyperplasia.4 Patients taking oral contraceptives tend to have larger, symptomatic lesions sometimes associated with haemangiomata.1 8

Oclusive lesions in small arteries and veins may also cause ischaemia followed by atrophy and regenerative nodules. In sickle cell disease blockage of small vessels by deformed red blood cells leads to tissue damage. Sequestration of sickled cells also lead to infarction. The resulting ischaemia and necrosis may provide an explanation for the development of focal nodular hyperplasia. Markowitz et al suggested that the primary abnormality may still be an underlying vascular anomaly and that ischaemia from sickle cell thrombosis acts as a stimulant to the development of focal nodular hyperplasia.2

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