CASE REPORT

Rapidly involuting congenital haemangioma of the liver

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SUMMARY

Rapidly involuting congenital haemangiomas (RICHs) are rare benign vascular tumours of infancy. They are generally asymptomatic, but can present with thrombocytopaenia and coagulopathy. Significant complications including life-threatening bleeding, high-output heart failure and liver failure, though rare, can occur. RICHs generally regress by 12–14 months of age and can be managed clinically with symptomatic treatment, watchful waiting and close monitoring of the size of the haemangioma. Medical management (corticosteroids, propranolol) has not shown to be effective, in contrast to infantile haemangioma which will not regress spontaneously and has been noted to respond to medical therapy. Awareness of this diagnosis is important to prevent unnecessary medical and surgical intervention. Here, we present a case of a full-term infant with RICH who presented with thrombocytopaenia and abnormal coagulation profile. The coagulopathy was treated symptomatically, while the lesion was observed with serial ultrasounds and gradually decreased in size.

BACKGROUND

Rapidly involuting congenital haemangiomas (RICHs) are rare benign vascular neoplasms of infancy which are generally asymptomatic. Hepatic RICH can be easily confused with other hepatic lesions, leading to potentially unnecessary medical and surgical interventions. Therefore, RICH should always be included among the differential diagnosis of isolated hepatic mass in newborn infants.

CASE PRESENTATION

A 3400 g male infant was born at 40 weeks' gestation to a 32-year-old primigravida mother at a community hospital. Mother was A+, antibody negative, with negative screening laboratories and group B *Streptococcus* culture negative. She had a history of herpes simplex virus (HSV) infection but no active lesions at the time of delivery, and otherwise had an uncomplicated pregnancy. Labour was complicated by prolonged rupture of membranes for 24 hours, foul-smelling amniotic fluid and maternal fever of 38.05°C.

The infant was delivered vaginally and had poor respiratory effort requiring 2 min of positive pressure ventilation, with Apgar scores of 4 and 8 at 1 and 5 min, respectively. After initial resuscitation, the infant was started on antibiotics due to concerns of maternal chorioamnionitis; as the infant was febrile to 38.6°C. Initial complete

blood count (CBC) at 24 hours of life (HOL) showed $14.2 \times 10^9/L$, 10% bands, 47% polymorphonuclear neutrophils (PMNs) and platelets of $73 \times 10^9/L$. Repeat platelet count on day of life (DOL) 3 was $59 \times 10^9/L$, and 6 hours later was $36 \times 10^9/L$, prompting transfer to a level III neonatal intensive care unit (NICU).

On admission to our hospital, the infant was well appearing, afebrile with stable vitals, with normal cardiopulmonary examination. The abdomen was soft, non-tender, with normal bowel sounds and a palpable mass about 1.5 cm below the subcostal margin in the left upper quadrant. Neurological examination was unremarkable. Skin examination showed no petechiae. Repeat platelet count on admission was $55 \times 10^9/L$, blood type A+ and Coombs negative. On DOL 4, patient developed new facial bruising and scattered petechiae, for which the infant received a 10 cc/kg platelet transfusion, following which platelet count increased to $174 \times 10^9/L$.

Abdominal ultrasound revealed a large, $5.4 \times 3.6 \times 5.0$ cm, heterogeneous, complex solid mass replacing the lateral segment of left hepatic lobe (figure 1). Abdominal MRI (figure 2) demonstrated a heterogeneous mass displacing the left pole of the liver. Differential diagnosis at this time included congenital haemangioma (CH), infantile haemangioma (IH), haemangioendothelioma, hepatoblastoma, germ cell tumour, neuroblastoma and mesenchymal hamartoma. Serum alpha-fetoprotein (AFP), serum quantitative beta-human chorionic gonadotropin (hCG) and urine catecholamines were sent on DOL 3. AFP level was significantly elevated at $>36\,300$ ng/mL, quantitative beta-hCG and urine for catecholamines levels were normal.

On DOL 5, the infant was found to have an abnormal coagulation profile with slightly prolonged activated partial thromboplastin time of 42.6 s, low fibrinogen level: 81 mg/dL (normal: 150–450 mg/dL) and abnormal D-dimer levels at 20.1 mg/L (normal: 0.19–<1.0 mg/L), requiring fresh frozen plasma and cryoprecipitate transfusion, leading to stabilisation of the coagulation profile. The coagulation profile completely stabilised by 16 days of age.

The remainder of the NICU course was uneventful with stable platelet count and coagulation profile. Based on the findings of initial coagulopathy, solitary liver mass and the appearance of the lesion based on MRI, a diagnosis of RICH was made. Tissue biopsy was not performed due to risk of bleeding from the vascular lesion.

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Figure 1 Abdominal ultrasound showing 5.4×3.6×5.0 cm, large, heterogeneous, complex solid mass replacing lateral segment of left hepatic lobe.

Infant was discharged home at 9 days of life with plans for close follow-up with both the paediatrician and paediatric haematologist. Serial laboratory evaluations have shown decreasing AFP levels, and serial abdominal ultrasounds have reported involuting size of the haemangioma.

INVESTIGATIONS

Abdominal ultrasound revealed a large, 5.4×3.6×5.0 cm, heterogeneous, complex solid mass replacing lateral segment of left hepatic lobe ([figure 1](#)). The lesion was noted to be hypoechoic relative to liver parenchyma, without definitive calcifications. Limited colour Doppler ultrasound was performed which showed internal vascularity though with most vessels being peripheral, and no evidence of thrombus. Abdominal MRI ([figure 2](#)) demonstrated a heterogeneous mass displacing the left pole of the liver. While the left portal and hepatic veins were not definitively identified, the remainders of the portal and hepatic veins were patent. MRI similarly showed predominantly peripheral enhancement with minimal central enhancement and no definitive calcifications. T1-weighted image immediately postintravenous gadolinium administration demonstrated peripheral

puddling of contrast material within the lesion. Serum AFP was significantly elevated at >36 300 ng/mL.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included CH, IH, haemangioendothelioma, hepatoblastoma, germ cell tumour, neuroblastoma or mesenchymal hamartoma.

TREATMENT

The initial thrombocytopenia and coagulopathy required a platelet, cryoprecipitate and a fresh frozen plasma transfusion. Subsequent NICU course was unremarkable. No active medical or surgical intervention was further pursued. Infant was discharged home with close follow-up with the paediatrician and paediatric haematologist.

OUTCOME AND FOLLOW-UP

Following the transfusions, the thrombocytopenia and abnormal coagulation profile resolved. The infant was discharged from the NICU at 9 days of life with close paediatric haematology

Figure 2 Left: Abdominal MRI demonstrating a heterogeneous mass displacing the left pole of the liver. Right: T1-weighted image immediately postintravenous gadolinium administration demonstrates peripheral puddling of contrast material within the lesion (arrows).

follow-up. Serial ultrasounds of the abdomen have demonstrated involuting haemangioma size; by age 14 months it had decreased to 3.1×3.1×3.4 cm, and continues to shrink. The haemangioma size is still being closely monitored for complete resolution by paediatric haematologist–oncologist. Serial AFP levels have also trended down gradually, following a classical RICH clinical picture.

DISCUSSION

Haemangiomas are benign vascular neoplasms of infancy. Recent understanding of the biology of these lesions has led to the division into two distinct categories, IH and CH. Of the two, CH is rarer with a combined incidence of less than 3% of the more commonly occurring nascent IH. The prevalence of IH in mature neonates is around 4.5%,¹ with a female (2.3–2.9 times higher) and white predominance.^{2,3} The lesions also differ in their clinical course. IH is typically small or undetectable at birth, grows rapidly in infancy and then gradually involutes.⁴ In contrast, the less common CHs are fully grown at birth then may shrink rapidly in early infancy and therefore are known as RICH, or do not involute and are therefore known as non-involuting congenital haemangioma (NICH). A very small number shows an intermediate pattern with partial involution.⁵ Positive immunohistochemical staining for glucose transporter protein-1 (GLUT1) reliably distinguishes IH in all its phases from CH, which almost uniformly stain negative for GLUT1.^{5,6} Some authors pose that focal IH should be considered to be hepatic RICH,⁷ as they also stain negative for GLUT1^{4,8} and as focal IH is uncommon during infancy, any focal hepatic haemangioma likely represents RICH.⁴

RICH and NICH differ in their structural make-up. NICHs are composed of large lobules of small vessels with intervening fibrosis, dermal arteriovenous microfistulae with large stellate vessels in the centre, hobnailed endothelial cells and thin basement membranes. In contrast, RICHs are composed of lobules of variable size with large extralobular vessels; the endothelium is plump and basement membranes is thicker.^{9,10} However, at the genetic level, nearly all CHs, both RICH and NICH, express activating mutations in the alleles which code for guanine nucleotide-binding protein G(q)α (GNAQ) and guanine nucleotide-binding protein subunit α-11 (GNA11). The varying clinical behaviour of these lesions with the same mutation (GNAQ and GNA11), implies that other genetic, epigenetic and/or environmental factors may influence these lesions' postnatal behaviour.¹¹

RICH can be further divided based on its location of involvement, either cutaneous or hepatic. Cutaneous RICH is a hypervascular lesion most frequently located on the scalp or extremities.^{5,12} Hepatic RICH may either manifest in the first weeks of neonatal life or may be detected antenatally on routine prenatal ultrasonography (US).

Hepatic RICH occasionally can be extremely vascular with high flow and can have direct arteriovenous and portal venous fistulas, leading to misdiagnosis as arteriovenous malformations (AVMs). However, the natural history of AVMs is eventual progression, not spontaneous resolution as in the case of RICH, particularly for such a large lesion as that reported by the authors.¹³ Arteriovascular shunting may rarely lead to high-output cardiac failure. If such shunting is extensive, a 'steal' phenomenon may occur which can affect other peripheral organs. This phenomenon may be treated in the short term with diuretics for symptomatic management, whereas definitive management is achieved with angioembolisation of the lesion.^{14,15}

RICH can be associated with a mild transient thrombocytopaenia and deranged coagulation profile which is self-limited and is expected to resolve by 2 weeks of age.^{16–18} The thrombocytopaenia in RICH may be a feature of larger lesions as it has never been reported in RICHs of smaller size.¹⁸ This consumptive coagulopathy is distinct from the Kasabach-Merritt syndrome, which is associated with profound thrombocytopaenia,¹⁹ fibrinogen consumption and secondary formation of D-dimer.²⁰ Disseminated intravascular coagulation²¹ and hepatic failure have been reported as rare complications of RICH.¹⁶ However, most of the time coagulation profile corrects with involution of the lesion. Transfusion is needed only in cases of symptomatic bleeding.^{22,23} In rare cases, RICH may be associated with life-threatening bleeding, which may be treated with embolisation or surgery.²²

The differential diagnosis of a liver mass in infants ranges from vascular malformations to benign and malignant tumours like mesenchymal hamartoma, hepatoblastoma and metastatic neuroblastoma.²⁴ Careful physical examination, imaging studies, tumour markers and biopsy are of pivotal importance to ascertain the correct diagnosis and exclude aggressive liver malignancies.²⁴ Furthermore, the differentiation of RICH from IH is important as management strategies are different. Misclassification of the mass as IH and result in unnecessary treatment of a self-resolving condition, as medical treatment also has its own risks.^{25,26}

Definitive diagnosis of RICH is achieved through biopsy, which histologically shows variably sized, though usually small, thin-walled vascular spaces, lined by bland endothelial cells without cytologically atypical features, with associated thrombosis and necrosis,^{27–29} and stain negative for GLUT1 transported protein.^{30,31} However, biopsy is invasive and presents a significant bleeding risk, especially in the presence of thrombocytopaenia or coagulopathy.

In lieu of biopsy the diagnosis may be suggested by the strikingly heterogeneous appearance on US, CT or MRI.^{32,33} The presence of a peripheral rim of enhancement (of variable thickness and irregularity) with little central enhancement on delayed images has been noted before in solitary liver haemangioma and suggests the diagnosis of RICH^{27,29,32,33} and was also observed in this patient. However, RICH may have overlapping radiographic features with both NICH and IH. All three may demonstrate fast flow at various stages during their natural history on ultrasound, and all may demonstrate a heterogeneous appearance on CT and MRI. While radiographic findings for RICH may overlap with IH and NICH, one helpful differentiating characteristic may be the presence of calcifications which are never present in IH but may be present in RICH and NICH. A second possibly useful marker is fat stranding on MRI, which is frequently seen in IH but not in RICH and NICH.⁹ Occasionally, RICH and NICH may be indistinguishable radiographically, and rather than specific features, a decrease in size of the lesion on subsequent imaging highly suggests a diagnosis of RICH. Of note, radiographic features including the presence of venous ectasia, venous lake or arteriovenous shunting may be associated with RICH and has been associated with increased risk of bleeding or high-output heart failure in these patients.³⁴

Serum AFP levels may also be helpful in establishing the diagnosis of RICH. Serum AFP can be elevated in normal newborn infant^{35,36} and can be higher in presence of a CH,^{37,38} however, while hepatoblastoma will continue to produce AFP, CH will not. Thus, it is recommended to perform serial measurements of AFP to document a falling serum AFP to rule out a hepatoblastoma. When there is no tumorous synthesis of AFP, serum levels fall very rapidly after birth in term neonates.⁴ Biopsy may

be deferred if the child has all three of the following: typical imaging features of RICH, regression on serial imaging and a falling serum AFP.⁴

Treatment of RICH is generally supportive as both the lesion and mild coagulopathy are anticipated to resolve without intervention.⁴ Corticosteroids have been trialled in past³⁹ and have not been shown to accelerate the natural involution of the lesion.⁴ Specific treatment like embolisation^{14 15} or surgical intervention might rarely be indicated in certain situations associated with uncontrolled active bleeding or heart failure. Treatment plan should be tailored according to individual clinical situation with a multidisciplinary approach with the vascular team, paediatric haematologist, dermatologist, paediatric surgeon and/or plastic surgeon as required based on individual lesion size, location and risk for complications. All patients will need close monitoring after discharge with serial radiographic imaging to monitor involuting size of RICH. Additionally, monitoring for active bleeding, and serial laboratories to evaluate for coagulation profile and platelet count should be considered if history of bleeding or abnormal laboratory findings are present. Parental education regarding natural history of the lesion, potential risk for complications and need for close monitoring and follow-up is of prime importance. Evidence from small case series and case reports indicates that most RICHs undergo complete regression in 12–14 months.^{40–42}

This case describes a rare diagnosis of hepatic RICH, which was identified with thorough physical examination, laboratory findings and classic appearance on imaging. Awareness and correct identification of RICH can prevent unnecessary invasive testing and treatment of an otherwise benign condition, as lesions may be successfully managed with symptomatic treatment and watchful waiting.

Learning points

- ▶ Rapidly involuting congenital haemangiomas are rare benign vascular tumours of infancy.
- ▶ They are typically asymptomatic but can cause a transient coagulopathy.
- ▶ Awareness of this diagnosis can prevent invasive tests or unnecessary medical treatment of an otherwise benign condition.

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