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Giant Hepatic Regenerative Nodule in a 17-year-old Woman with Alagille Syndrome: A Case Report

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Abstract: Alagille Syndrome is a multisystem genetic disorder characterized by paucity of intrahepatic bile ducts, which can lead to early cirrhosis and an increase in the risk of developing focal liver lesions, including hepatocellular carcinoma. Therefore, patients with Alagille syndrome are often followed with routine imaging surveillance. However, it can be challenging to distinguish incidentally found benign liver tumors from their malignant counterparts in this subset of patients. Here we present the case of a giant regenerative hepatic nodule in a 17-year-old woman with Alagille syndrome. The case is presented with associated imaging studies that favored a diagnosis of benign hyperplasia, confirmed by the results of histologic examination.

Keywords: Alagille syndrome; giant regenerative hepatic nodule; MRI characteristics

Case Presentation

In August 2019, a 17-year-old woman with Alagille syndrome (AGS) was referred to interventional radiology at UCLA for biopsy of a liver mass. This patient was initially diagnosed with AGS at 3 months of age, after an open liver biopsy at Children's Hospital of Los Angeles, in the setting of persistent jaundice and failure to thrive. The patient's early clinical course was complicated by severe persistent pruritus refractory to hydroxyzine, and in September 2003, at age 23 months, the patient underwent biliary diversion with ileal exclusion surgery to palliate her pruritus symptoms. At that time, a preoperative ECG revealed diffuse hypoplasia of the left branch of pulmonary artery with moderate stenosis but no other major congenital cardiac abnormalities. Approximately a month after initial surgery, the patient's clinical course was further complicated by intussusception of the defunctionalized ileal limb, requiring ileocecectomy with primary

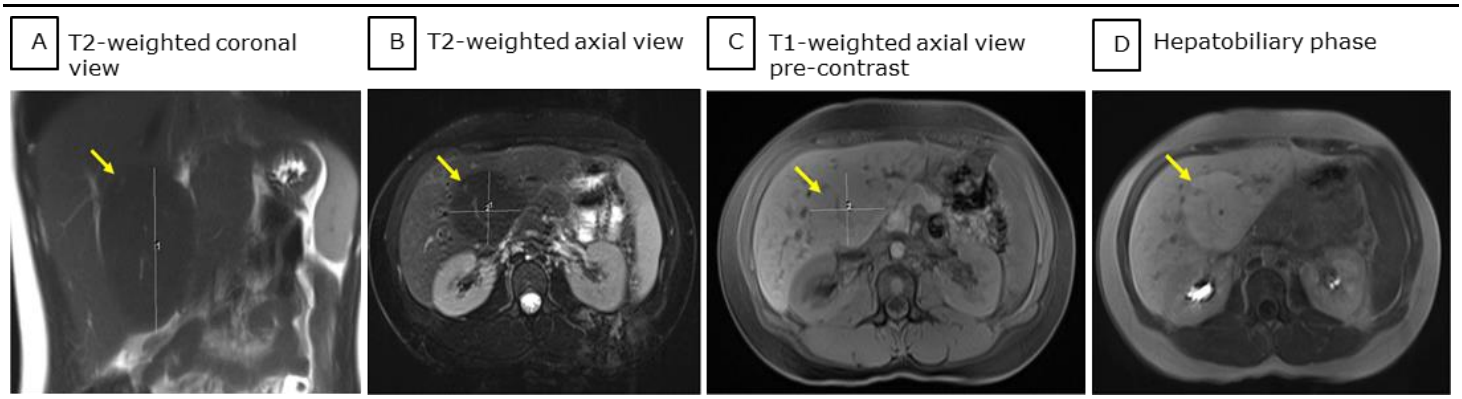
Key Points

- Alagille Syndrome can lead to childhood cirrhosis. Therefore, patients with AGS are at increased risk of developing HCC and require routine imaging surveillance.
- Regenerative hepatic nodules described in AGS have distinctive MR attributes, including variable intensity (often isointensity) on T1-weighted images, isointensity or hypointensity on T2-weighted images, enhancement patterns similar to those of surrounding normal liver parenchyma, and lack of diffusion restriction.
- Attention to these MRI features may help distinguish benign giant regenerative nodules from HCC, avoid unnecessary interventions, and provide guidance for further management of patients with AGS.

anastomosis. One year later, in 2004, the patient presented with abdominal pain and vomiting. CT and ultrasound of the abdomen, at that time, revealed only hepatomegaly and possibly some constipation.

Because of the paucity of intrahepatic bile ducts and chronic cholestasis, patients with AGS are at increased risk of developing cirrhosis and hepatocellular carcinoma (HCC).[1-4] Therefore, these patients typically undergo routine surveillance imaging. Our patient underwent a surveillance MRI with gadoxetate disodium (Eovist) contrast in September 2017 to rule out incidental HCC. The examination revealed a new T2-weighted hypointense and T1-weighted isointense, well-circumscribed mass occupying segment V of the liver and measuring 5.3 x 5.9 x 10 cm (Figure 1A-C). On hepatobiliary phase

Figure 1. A Series of Surveillance Magnetic Resonance Images (September 2017) of Abdomen with Gadoxetate Disodium.



T2-weighted coronal (A) and axial (B) images show a 5.3 x 5.9 x 10 cm well-circumscribed hypointense mass (A and B, arrows) occupying segment V of the liver. Axial T1-weighted pre-contrast image (C) shows an isointense mass (C, arrow). Notably, on post-contrast images, not included here, the mass demonstrates enhancement characteristics similar to those of the normal adjacent liver parenchyma. On hepatobiliary phase image (D), 22 minutes after gadoxetate disodium administration, the mass (D, arrow) remains hyperintense compared to background liver parenchyma. Overall, these imaging features favor benign giant regenerative nodule.

imaging, the mass remained hyperintense compared with background liver and was thought to represent a giant regenerative hepatic nodule (Figure 1D).

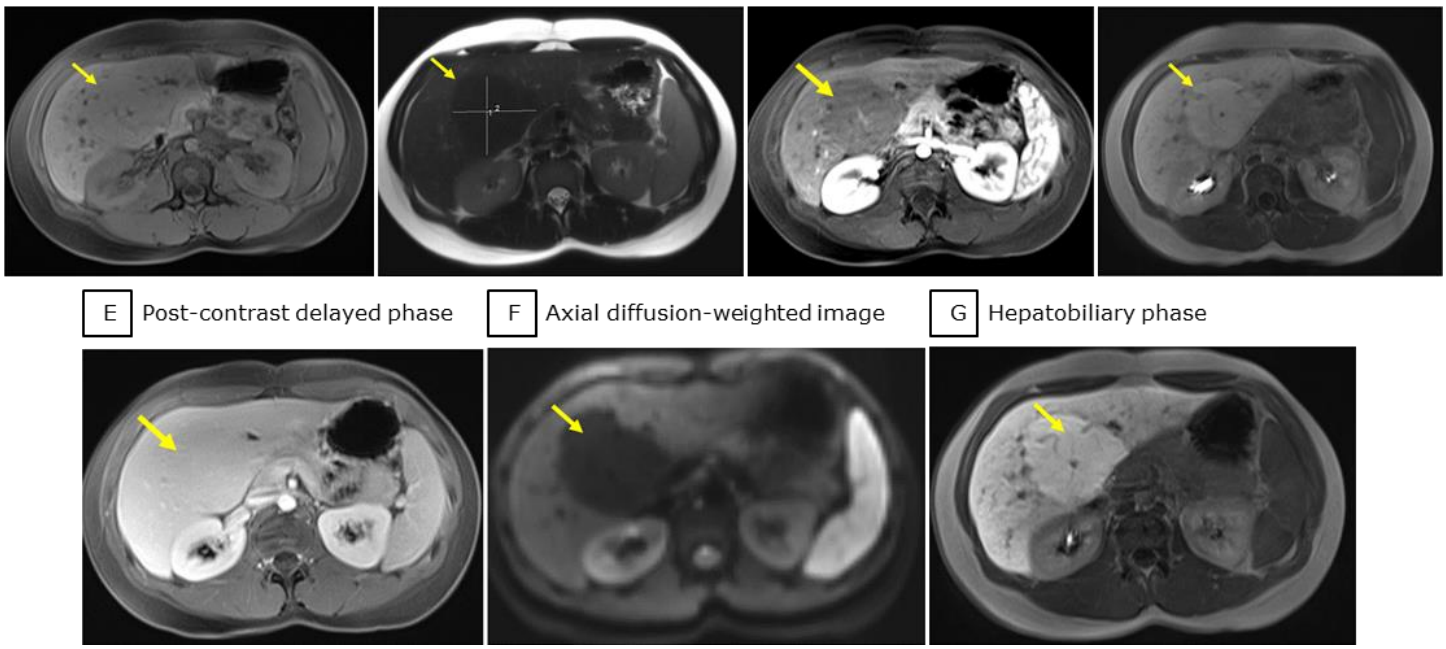
In December 2018, a second surveillance MRI with gadoxetate disodium showed slight interval enlargement of the mass, now measuring 6.0 x 6.1 x 10 cm (Figure 2). The mass again appeared slightly hypointense on T2-weighted images and isointense on T1-weighted images, with enhancement characteristics similar to those of the normal adjacent liver parenchyma and normal vessels branching through the lesion (Figure 2A-E). Similar to the imaging study performed in 2017, this study demonstrated no evidence of restricted diffusion on diffusion-weighted images (Figure 2F). On hepatobiliary phase images, there was redemonstration of persistent hyperintensity of the mass compared with background liver (Figure 2G). Again, these characteristics taken together favored a giant regenerative nodule in the setting of AGS.

Although imaging results were suggestive of a diagnosis of benign hyperplasia and alpha-fetoprotein levels remained normal, HCC was still on the list of diagnostic considerations. Therefore, the patient was referred to interventional radiology for biopsy to establish a tissue diagnosis. Ultrasound-guided core biopsy was performed in August 2019. Procedural ultrasound showed a round hepatic mass with mildly hypoechoic echogenicity compared to surrounding parenchyma (Figure 3). Histologic examination revealed benign hepatocytes, mild patchy sinusoidal dilatation, minimal iron deposition, and presence of bile ducts, but no evidence of malignancy or atypical features.

Discussion

AGS is an "autosomal dominant multisystem condition" characterized by the association of cholestasis with a wide spectrum of clinical

Figure 2. A Second Surveillance MRI (December 2018) of Abdomen with Gadoxetate Disodium.



Again seen is a segment V liver mass (A, arrow); isointense on T1-weighted image (A), slightly hypointense on T2-weighted image (B, arrow), and now measuring 6.0 x 6.1 x 10 cm. Axial post-contrast early hepatic arterial (C), late hepatic arterial (D), and delayed phase images (E) show the mass (C, D, and E, arrows) having an overall enhancement pattern similar to that of normal adjacent liver parenchyma. Of note, the mass (C, arrow) demonstrates very mild hypoenhancement compared to surrounding liver in early arterial phase (C). There is no evidence of restricted diffusion of the mass (F, arrow) on diffusion-weighted image (F). Overall, these imaging features favor benign giant regenerative nodule (F, arrow). On hepatobiliary phase image (G), 19 minutes after gadoxetate disodium administration, the mass (G, arrow) remains hyperintense compared with background liver parenchyma.

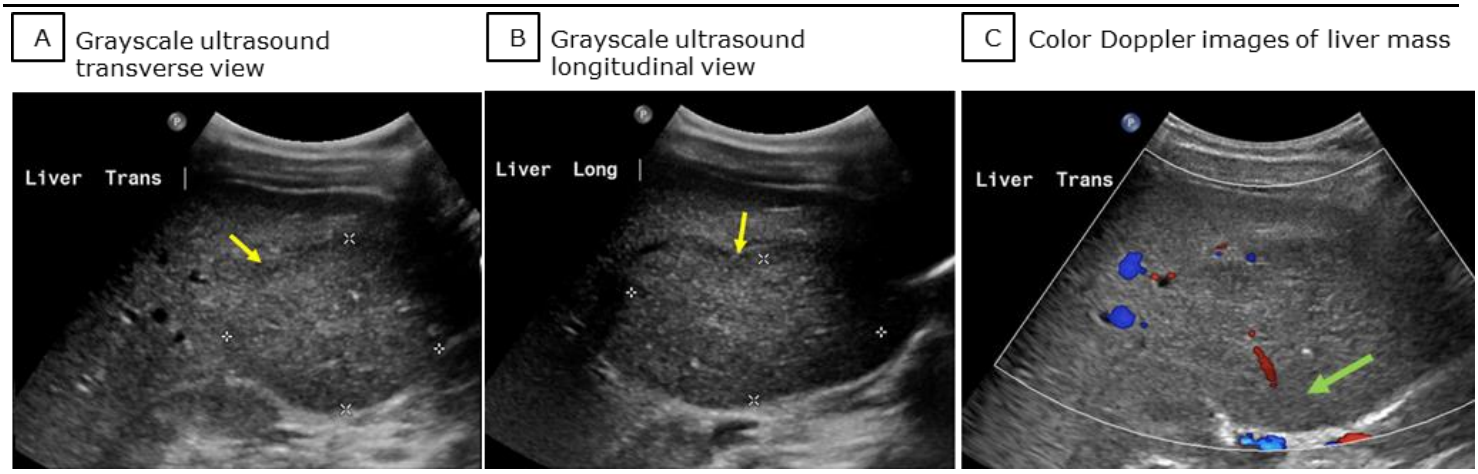
features most commonly involving cardiac, vertebral, ocular, facial, or renal anomalies.[2,3] The disease frequency is approximately 1 in every 30,000 newborns, and most patients with AGS have mutations in *JAG-1* gene.[3] Initial evaluation of these patients includes laboratory tests and liver imaging, and the diagnosis is typically confirmed by histologic examination and genetic studies.[4]

Paucity of intrahepatic bile ducts in this condition can lead to cholestasis in infancy and, over time, to chronic liver disease of varying severity, including frank cirrhosis in up to 20% of patients, sometimes requiring liver transplant.[5] Cirrhosis in these cases, as in other forms of fibrotic liver disease, increases the risk of developing HCC and requires frequent imaging surveillance of patients with AGS to detect malignant masses.[4-7] Yet, hepatic regenerative nodules and other benign hepatic masses can also occur in this subset of patients, and it is important to recognize imaging characteristics that may help distinguish these lesions from their malignant counterparts, such as HCC.[7]

Regenerative nodules are classified as micronodules if they are less than 3mm in size; those that are greater than 3 mm are classified as macronodules.[8] Giant regenerative nodules with diameter >5 mm are rare in the setting of AGS, and only a few such cases are reported in the literature.[7,8] In 2017, Rapp et al[7] presented a case series of AGS in 6 patients who had giant regenerative nodules that demonstrated benign ultrasound and MRI findings, long-term stability, and, in almost all cases, corresponding benign results of histologic examination.

In this report, we have described a case of AGS in a patient with a 10cm liver mass that was isointense to surrounding parenchyma on T1-weighted images, slightly hypointense on T2-weighted images, and with a contrast-enhanced MRI pattern similar to that of normal adjacent liver parenchyma. Most importantly, in both MRI studies the mass remained hyperintense

Figure 3. Procedural Ultrasound Exam Performed during Image-Guided Core Needle Biopsy.



Transversal (A) and longitudinal (B) images of the liver demonstrate a clearly distinguishable round mass (A and B, yellow arrows and white asterisks) with mildly hypoechoic echogenicity compared to the surrounding liver parenchyma. Color Doppler image (C) of the liver mass suggests mild internal vascularity (C, green arrow).

compared with background liver on hepatobiliary phase images, a feature that is characteristic of benign hyperplasia and critical for distinguishing the mass from HCC.[8,9] The lesion did not demonstrate any classic imaging characteristics associated with HCC, such as arterial hyperenhancement or venous phase "washout" of contrast material.[9] Nor did it show diffusion restriction on diffusion-weighted imaging, again, favoring a benign lesion over HCC, which typically restricts diffusion.[9] Overall, the imaging features demonstrated by this mass favored a diagnosis of a giant regenerative hepatic nodule. Furthermore, our ultrasound and MRI findings are very similar to those described by Rapp et al[7] in their aforementioned case series. Finally, our patient's tissue histologic examination revealed mild patchy sinusoidal dilatation in otherwise normal hepatic architecture, notably with preservation of well-formed bile ducts, again remarkably similar to the findings described in the report by Rapp et al.[7]

In summary, Alagille syndrome is a rare genetic condition that can lead to cirrhosis in children, predisposing them to development of focal liver lesions, including HCC. Previous reports in the literature, further supported by our case report, suggest that described MR imaging criteria may be used to reliably characterize these lesions and distinguish benign masses, such as giant regenerative nodules, from HCC. These criteria may help mitigate the need for interventions and provide guidance for further management of patients with AGS.

Author Contributions

Conceptualization, A.L., P.I. and S.M; Writing – original draft preparation, S.M.; Review and editing, S.M., P.I. and A.L.; Supervision, A.L. and P.I. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

References

1. Kim B, Park S-H, Yang HR, Seo JK, Kim WS, Chi JG. Hepatocellular carcinoma occurring in Alagille syndrome. *Pathol Res Pract*. 2005;201(1):55-60. doi.org/10.1016/j.prp.2004.11.007
2. Kamath BM, Baker A, Houwen R, Todorova L, Kerkar N. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. *J Pediatr Gastroenterol Nutr*. 2018;67(2):148-156. doi: 10.1097/MPG.0000000000001958
3. Hartley JL, Gissen P, Kelly DA. Alagille syndrome and other hereditary causes of cholestasis. *Clin Liver Dis*. 2013;17(2):279–300. doi: 10.1016/j.cld.2012.12.004
4. Wetli SC, Gralla ES, Schibli S, Stranzinger E. Hepatocellular carcinoma and regenerating nodule in a 3-year-old child with Alagille syndrome. *Pediatr Radiol*. 2010;40(10):1696–1698. doi: 10.1007/s00247-010-1784-6
5. Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut.* 2001;49(3):431–435. doi: 10.1136/gut.49.3.431

6. Tajima T, Honda H, Yanaga K et al. Hepatic nodular hyperplasia in a boy with Alagille syndrome: CT and MR appearances. *Pediatr Radiol*. 2001;31(8):584–588. Doi: 10.1007/s002470100510
7. Rapp JB, Bellah RD, Maya C, Pawel BR, Anupindi SA. Giant hepatic regenerative nodules in Alagille syndrome. *Pediatr Radiol.* 2017;47(2):197-204. doi: 10.1007/s00247-016-3728-2
8. Hanna RF, Aguirre DA, Kased N et al. Cirrhosis-associated hepatocellular nodules: correlation of histopathologic and MR imaging features. *Radiographics.* 2008;28(3):747–769. doi: 10.1148/rg.283055108
9. Lee MH, Kim SH, Park MJ, Park CK, Rhim H. Gadoxetic acid–enhanced hepatobiliary phase MRI and high-b-value diffusion-weighted imaging to distinguish well-differentiated hepatocellular carcinomas from benign nodules in patients with chronic liver disease. *AJR Am J Roentgenol.* 2011;197(5):W868-875. doi: 10.2214/AJR.10.6237