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Original research Articles

Large Regenerative Nodule in Alagille Syndrome – A Case Report

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Abstract:- Alagille Syndrome is a rare complex multisystem genetic disorder with a wide spectrum of clinical findings. Hepatic involvement in Alagille is characterized by paucity of intrahepatic bile ducts, which often presents with cholestasis and can rarely lead to cirrhosis and hepatic failure requiring liver transplantation. Liver nodules in Alagille can range from benign regenerative to dysplastic nodules and rarely hepatocellular carcinoma. The typical imaging findings of a regenerative nodule on cross sectional imaging can avoid unnecessary biopsy. Here, we present the case of a large regenerative hepatic nodule in Alagille syndrome with typical imaging findings who underwent hepatic transplantation at 9 years due to hepatic failure and histopathology was confirmed on explant liver.

Keywords: Alagille Syndrome, Liver nodules, Cholestasis, Cirrhosis, Hepatic transplantation.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to authorized users.

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Introduction:

Alagille syndrome (ALGS), also recognized as arteriohepatic dysplasia, Alagille-Watson syndrome, Watson-Miller syndrome, or syndromic bile duct paucity, is a complex autosomal dominant disorder that affects multiple systems, displaying a wide spectrum of clinical manifestations. Estimated prevalence of Alagille syndrome varies from 1:30,000 to 1:100,000 [1]. The disease is most often attributed to one of several identified mutations in the Jagged1 (JAG1) gene, which encodes for Notch1. Notch proteins are ubiquitously expressed signaling proteins which are thought to be involved in the cell fate determination in a wide variety of tissues in humans and in other organisms [2].

Case History:

A nine-year-old girl, known case of Alagille syndrome presented with complaints of abdominal pain and distension. She is the 2nd child of non-consanguineous marriage, developed prolonged jaundice at 6 weeks of age.

Chol scintigraphy (HIDA scan) was suggestive of biliary atresia and hence was taken up for Kasai procedure. Intraoperative cholangiogram showed paucity of bile ducts and ruled out biliary atresia. Liver biopsy showed marked intrahepatic and canalicular cholestasis, feathery degeneration of hepatocytes and mild infiltrate in portal triad with normal bile duct and no cirrhosis. As per biopsy report, she was suspected to have Alagille syndrome. Echo showed peripheral pulmonic stenosis. Genetic study showed JAG1 mutation, and she was confirmed to have Alagille syndrome. On further follow up, at 9 months of age, peculiar facial features such as triangular face and xanthomas became evident. All her developmental milestones were normal. Detailed workup was done to look for associated anomalies. Chest radiograph revealed butterfly vertebra at D1 to D5 level. MRI brain showed scaphocephaly and herniation of peg like cerebellar tonsils 13mm below level of foramen magnum with reduced volume of posterior fossa, suggestive of Chiari I malformation. MR cerebral angiogram revealed narrowing of bilateral supraclinoid ICA, described in Alagille syndrome **(figure 1 a,b,c)**.

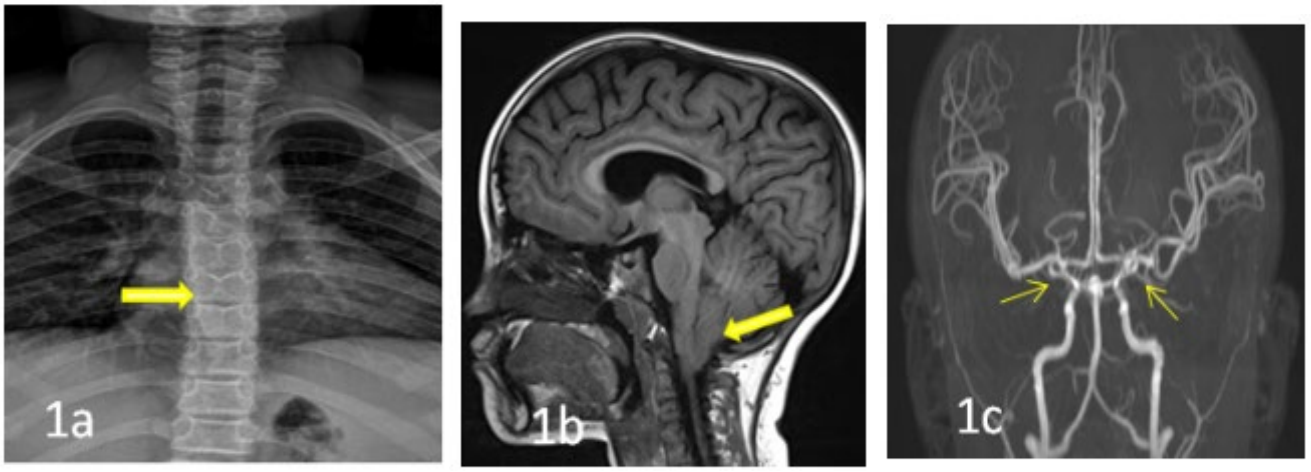


Figure 1 - (1a) Frontal radiograph of thoracic spine showing Butterfly vertebra (arrow) D1-D5. (1b) Sagittal T1W MR brain showing Scaphocephaly, peg like tonsillar herniation (arrow) Chiari 1 malformation. (1c) MR angiogram showing narrowing of supraclinoid ICA on both sides (arrow).

Laboratory tests showed elevated bilirubin and liver enzymes with normal coagulation parameters (Bilirubin Total/Direct-4/3, AST- 577,ALT-244, ALP-196). Serum ferritin level was 666 microgram/litre (normal range is 52-421) and alpha-feta protein was 268 microgram/liter (normal range is 0-15.4). Ultrasound abdomen revealed moderate sized isoechoic liver lesion in a background of cirrhosis with moderate splenomegaly and ascites **(figure 2)**.

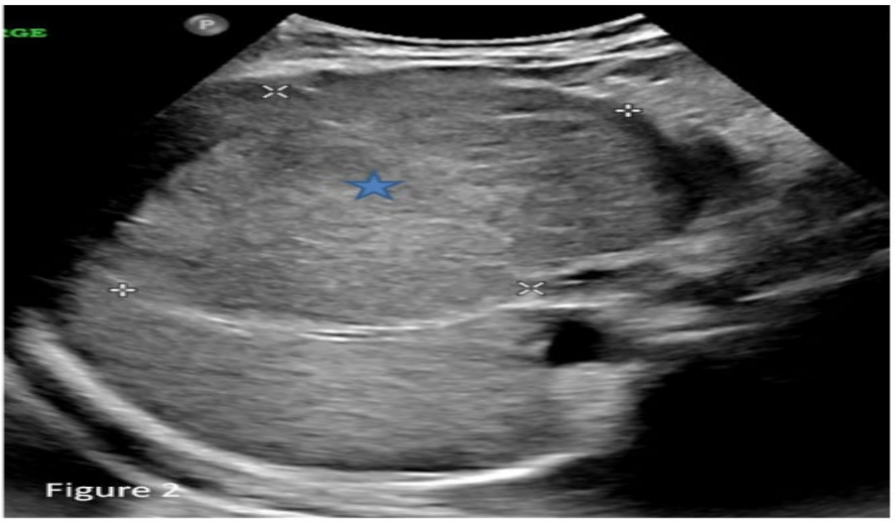


Figure 2 - Ultrasound liver showing well marginated isoechoic nodule (star) in right lobe of liver.

MRI was done further to characterize the lesion. MRI abdomen showed moderate sized mass involving central compartment of liver with lobulated contour and significant exophytic component in subhepatic region compressing the hepatic hilar structures. This lesion measures 8.6 x 12.5 x 6.7 cm (AP X TR X CC) involving segment IV, V, VI, VIII and caudate lobe of liver.

The lesion is mildly T1 hyperintense, T2 hypointense with no enhancement on post contrast subtracted arterial , venous and delayed phases. Another similar characteristic small lesion was noted in segment 8. Background liver showed heterogenous attenuation and volume redistribution with moderate splenomegaly and ascites suggestive of underlying chronic liver disease **(figure 3 and figure 4 a,b,c,d,e,f)**.

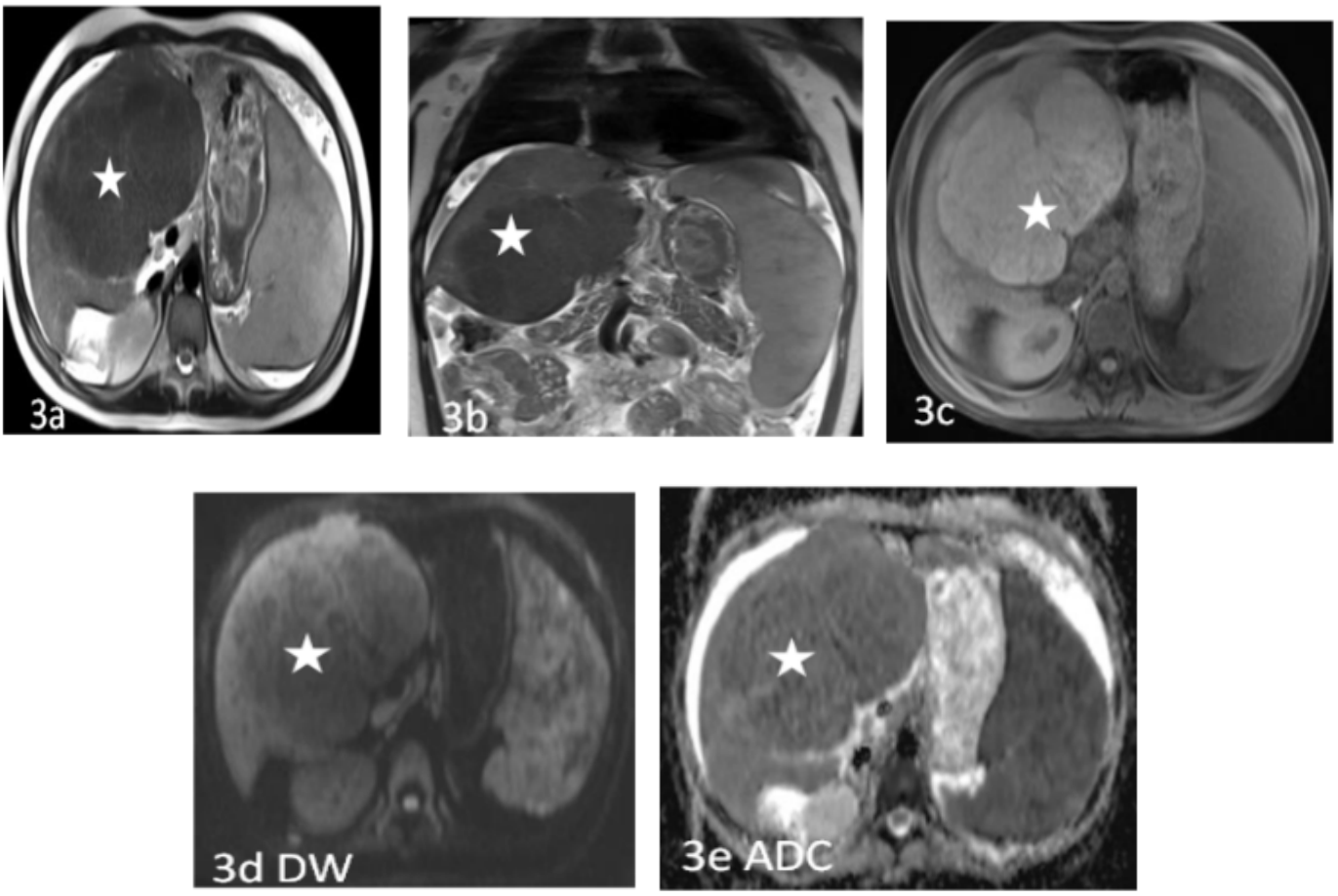
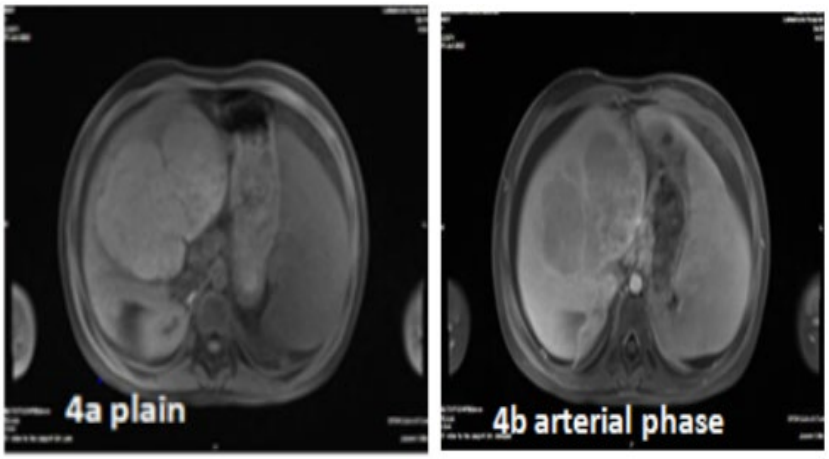


Figure 3 – MR abdomen T2 W axial and coronal images (a,b) showing hypointense nodule star) with mild hyperintensity in T1W sequences (c) with no diffusion restriction (d,e).



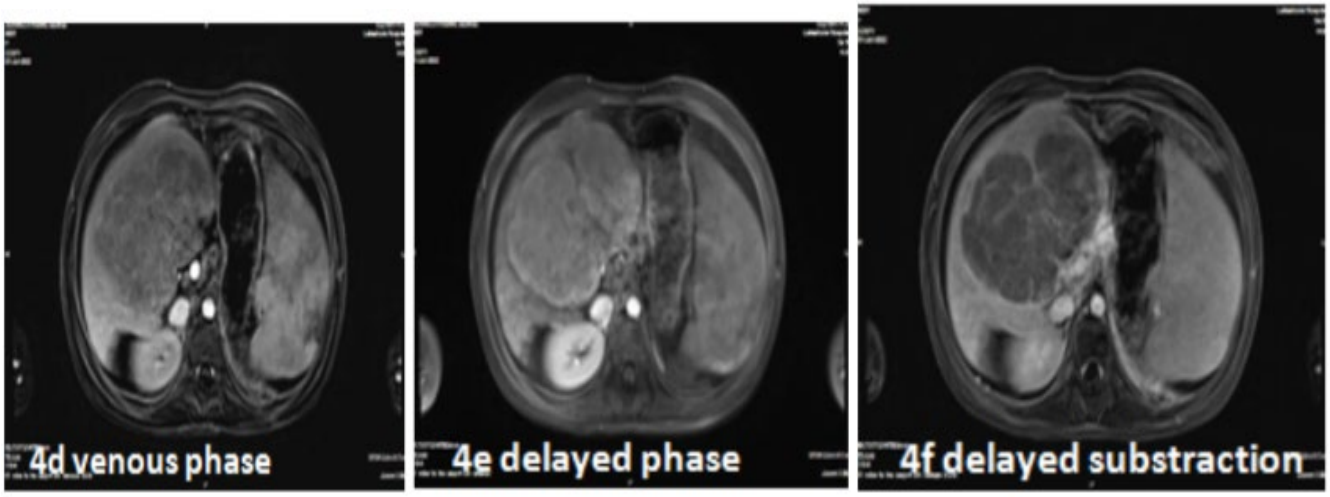
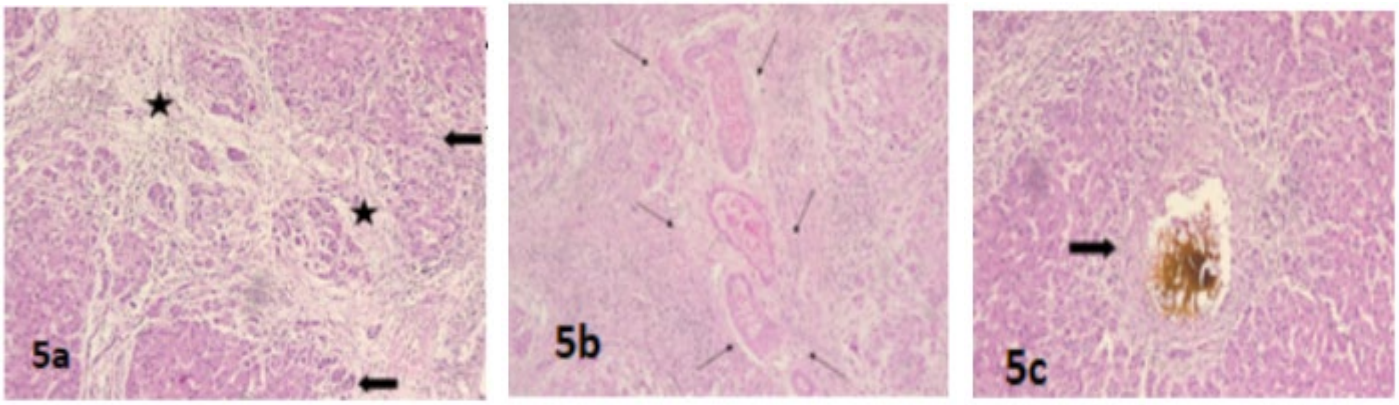


Figure 4 – Axial MRI T1W plain and contrast (Arterial, venous delayed with substraction) imaging showing no enhancement of nodule suggesting regenerating nodule. (a – plain, b – arterial phase, c – arterial phase substraction, d – venous phase, e – delayed phase, f – delayed phase substraction)

In view of progressive deterioration of liver function in spite of medical management, the child was taken up for hepatic transplant. Histopathology of explant liver showed cirrhosis with large regenerative nodule and paucity of bile ducts, favoring Alagille syndrome **(Figure 5 a,b,c,)**.



CK19 IHC shows absent bile ducts in portal areas (arrows showing portal area **(Figure 5 d)**. Post transplant the child is on regular follow up with normal liver functions.

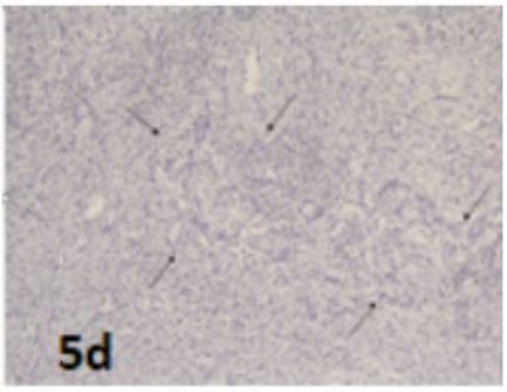


Figure 5 – Low power view showing disorganized hepatic lobular architecture by bridging bands of fibrosis (star in 5a) separating nodules of hepatocytes (arrow). Portal areas (arrow in 5b) showing absent interlobular bile ducts. 5c shows bile lakes (arrow). CK19 IHC shows absent bile ducts in portal areas (arrows showing portal area in 5d).

Discussion :

The clinical presentation of Alagille syndrome can vary significantly, even within the same family ranging from mild or asymptomatic to severe and potentially life-threatening conditions. Alagille syndrome is diagnosed when an individual has three out of seven major clinical features.

The seven major clinical features include:

1. Hepatic (cholestasis, characterized by bile duct paucity on liver biopsy),
2. Cardiac (primarily involving the pulmonary arteries),
3. Skeletal (butterfly vertebrae, hemivertebra),
4. Ophthalmologic (posterior embryotoxon),
5. Dysmorphic facies (triangular face with a pointed chin, hypertelorism, prominent ears, and broad nasal bridge),
6. Renal dysplasia and
7. Vascular abnormality.

Studies have indicated a mortality rate of up to 10% associated with this syndrome **[1]**. The factors that contributed significantly to mortality were complex congenital heart disease (15%), intracranial bleeding (25%), and hepatic disease or hepatic transplantation (25%) **[2]**.

Hepatic involvement of Alagille syndrome usually presents with cholestasis, conjugated hyperbilirubinemia, pruritus, xanthomas and rarely cirrhosis leading to end-stage liver disease in up to 15% of the cases. The characteristic liver pathology in Alagille syndrome is interlobular bile duct paucity. Bile duct paucity is present in 75- 100% of the cases **[3]**. However bile duct paucity is no longer considered mandatory for the diagnosis of Alagille syndrome, the presence of cholestasis can be used instead. Alagille **[4]** describes a ratio of the number of interlobular bile ducts to the number of portal tracts of less than 0.4 and recommends examining at least 10 portal tracts to derive this ratio.

Hepatic nodules in Alagille can range from benign regenerating nodules to more dysplastic nodules and even hepatocellular carcinoma. There are several reports of concomitant hepatocellular carcinoma and large regenerative nodule (LRN) in the literature **[5-7]**. Various nomenclatures have been employed to describe these benign hepatic nodules, from “pseudotumoral hyperplasia” to “nodular macroregenerative tissue” **[8]**. The most consistent term has been either regenerative or regenerating nodules **[5]**. A regenerative nodule is defined as one that contain more than one portal tract, located in a liver that is otherwise abnormal, either with cirrhosis or with severe disease of portal veins, hepatic veins, or sinusoids. When multiacinar regenerative nodules are distinctly larger than at least 5 mm in diameter, they may be called large regenerative nodules or macroregenerative nodule. Large regenerative nodules usually measure 5 to 15 mm in diameter, but rarely may be 5 cm or more in diameter leading to irregular liver contour. Large regenerative nodules are often adjacent to large portal systems causing

portal hypertension due to portal vein obstruction. Color and texture are usually similar to surrounding liver, although the nodules may be paler or more bile stained **[9].**

Two recent case series by Alhammad et al. **[10]** and Rapp et al. **[11]** report a frequency of 30% for these lesions, in cohorts of 39 and 45 genetic proven cases of Alagille syndrome.

LRNs in patients with Alagille syndrome are often incidental imaging findings in younger patients. These patients may present with signs of portal hypertension (variceal bleeding and progressive hepatosplenomegaly) or cholestasis **[11]**. Alpha-fetoprotein (AFP) values, when available, are within normal limits in cases of regenerative nodules without concurrent hepatocellular carcinoma **[10]**.

Limited evidence exists to definitively ascertain the cause of regenerative hepatic nodules. Rougemont and McLin **[11]** suggest that vascular irregularities in cholestatic liver disorders lead to a preferential blood flow to central areas, resulting in the preservation of relatively normal bile ducts within this region of the liver. Conversely, Libbrecht and Cassiman **[12]**, along with Roberts et al **[8]**, propose that the central bile ducts in Alagille syndrome (and other cholestatic processes) possess an intrinsic capacity for preservation, allowing for a reactive response that occasionally manifests as a mass-like lesion. Consensus exists that the pathogenesis of the central nodules observed in Alagille syndrome and other cholestatic conditions is reactive in nature, as opposed to being neoplastic **[8, 11]**.

Macroscopically, LRNs in Alagille syndrome show a large, well-circumscribed hyperplastic nodule that is distinguished from the surrounding parenchyma **[11]**. 5 out of 11 cases of regenerative hepatic nodules identified by Alhammad et al. **[10]** had background hepatic cirrhosis. Roberts et al. **[8]** reviewed the incidence of regenerative liver nodules in patients in different cholangiopathic disorders and found that the nodules in Alagille syndrome tend to be more clearly demarcated compared to others. Histologic examination of LRNs shows a non-encapsulated hepatic lesion with generally preserved architecture and interlobular bile ducts with less fibrosis and more portal tracts compared to the surrounding parenchyma.

LRN are generally solitary lesions located in central compartment of liver usually associated with the portal vein **[10, 11]**. The nodule size vary from as small as 1.6cm in literature to 13.2cm **[8]**. On ultrasound, they appear isoechoic **[7, 11]**. CT scans often demonstrate iso to hyperdense lesion in a background of a cirrhotic liver **[9, 10]**. The MR signal intensity is inconsistent between different reports, but most often they are seen as hyperintense on T1 and hypointense on T2 sequences **[6,7]**. Radionucleotide scans with hepatobiliary agents show increased uptake within the lesions to varying degrees owing to compensatory hyperplasia/regeneration of the liver parenchyma in these lesions **[13, 14]**. Normal-appearing vessels may be seen coursing through the nodules **[6, 10]**.

The primary differential diagnosis for LRNs in Alagille syndrome is HCC. Few differentiating features of HCC include elevated serum AFP and imaging characteristics **[15]**. On imaging HCC appear hypoechoic or hyperechoic on ultrasound **[7]** and on cross-sectional study early enhancement and washout in delayed phases may be seen **[7]**. Moreover, there are several reports of concomitant hepatocellular carcinoma and LRN in the literature **[5-7]**.

LRNs in Alagille syndrome usually remain stable for years **[10]**. Up to 50% of patients with regenerative nodules showed an average increase in volume by 20 cm^3 over an average of 38.5 months as per Robert et al **[8]**. It is the background hepatic injury progressing to cirrhosis which may necessitate liver transplant in patients with Alagille

syndrome as in our case **[13, 14]**. Literature search shows that 15% to 47% of patients with Alagille syndrome had a transplant and the median ages at which patients underwent surgery ranged from 4 to 6.5 years **[3]**.

Conclusion :

Large regenerative nodule presenting as hepatic masses is an important diagnostic consideration in patients with Alagille syndrome. These lesions are usually solitary and centrally located and lies in close relation to portal vein with vessels coursing through the nodules Knowledge of typical imaging findings of regenerative nodule in cross-sectional imaging helps in accurate diagnosis avoiding unnecessary percutaneous biopsy.

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Statement and Declarations:

Ethical Statement: The authors are accountable for all aspects of the work (if applied, including full data access, integrity of the data and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.