

ATM Germline Mutations and Liver Adenomas in Adolescents: A Clinical Reminder

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An adolescent patient with hepatocellular carcinoma arising from a hepatic adenoma had both an ARID1A tumor mutation and a germline ATM mutation. This unique case, detailed in a recent publication, highlights the need for clinicians to consider genetic screening in young patients lacking typical HCA risk factors.

KEY TAKEAWAYS

- lightbulb
- The Pivot: In young patients with HCAs, particularly with no clear risk factors, consider underlying germline mutations like ATM. Don't default to lifestyle factors alone.
- The Data: This case showed that HCAs with ARID1A mutations may indicate an underlying DNA repair deficiency, specifically ATM germline mutation.
- The Action: If a young patient presents with HCA, obtain a detailed family history and consider referral for genetic testing, especially if ARID1A mutations are present in the tumor.

An adolescent had hepatocellular carcinoma (HCC) from a hepatic adenoma. No typical risk factors for HCA existed, such as oral contraceptive or anabolic steroid use. Doctors found an ARID1A mutation in the tumor. A subsequent ATM germline mutation in the patient was also identified. That prompted a deeper look. The case makes a clear argument: doctors need to think about germline mutations in young patients with atypical liver tumors. ARID1A mutations in a tumor could be a red flag for genetic evaluation.

Hepatic adenomas are rare, benign liver tumors. They mainly affect women of reproductive age, often tied to oral contraceptive use. HCAs are even rarer in adolescents. Their cause is often unclear, so finding genetic predispositions matters. HCA transforming into HCC is uncommon but serious. Larger adenomas or those with specific molecular profiles carry higher risk. The ARID1A mutation in the tumor is important because ARID1A is part of the SWI/SNF chromatin remodeling complex. Mutations in this gene appear in various cancers, including some liver tumors. Then came the germline ATM mutation. ATM is critical for DNA damage response and cell cycle control, with germline mutations tied to higher cancer susceptibility.

Existing guidelines miss a crucial piece. American Association for the Study of Liver Diseases (AASLD) guidelines, for instance, focus on HCC in cirrhotic or chronic hepatitis patients. They do not detail HCA approach in adolescents, nor the role of germline genetic testing. This case reveals a clear gap. AASLD does suggest considering liver biopsy for atypical lesions. But specific guidance on when to pursue genetic testing is absent. Long-term management and family

screening have big implications. Adding genetic evaluation recommendations for young HCA patients, especially those with ARID1A mutations or no typical risk factors, would improve protocols. EASL guidelines classify hepatic adenomas more by molecular markers. Still, they too lack specific guidance on germline testing in adolescents with HCA.

The single case report is the obvious caveat. Identifying the ATM germline mutation is important, yes. But it does not establish cause and effect between ATM mutations and HCA development in adolescents. Larger cohort studies are needed. The prevalence of ATM mutations in the broader adolescent HCA population also remains unclear. Routine genetic testing's clinical utility is hard to estimate without such data. And the cost-effectiveness of widespread genetic screening for ATM and other DNA repair genes in young HCA patients? Unknown.

The molecular characterization could also go deeper. While ARID1A and ATM mutations were found, a full genomic profiling might show other genetic alterations. The precise mechanism linking an ATM germline mutation to HCA or HCC with an ARID1A somatic mutation needs more work. The lack of long-term follow-up also leaves questions unanswered. This data would be crucial for understanding the natural history of ATM-associated liver lesions and surveillance efficacy.

The next trial must determine the true prevalence and clinical impact of ATM germline mutations in this young patient population.

Despite these limitations, the case underscores the evolving understanding of liver tumor etiology. The traditional paradigm, heavily reliant on environmental factors and chronic liver disease, is clearly insufficient for a subset of patients, particularly adolescents. This shift necessitates a broader diagnostic lens, integrating genetic insights earlier in the diagnostic pathway for atypical presentations.

Future Directions and Clinical Recommendations

Moving forward, multidisciplinary collaboration between hepatologists, oncologists, and genetic counselors will be paramount. Establishing a national or international registry for adolescent HCA cases could facilitate the collection of crucial data on germline mutations, tumor molecular profiles, and long-term outcomes. Such a registry would provide the statistical power needed to determine the true prevalence and penetrance of genes like ATM in this population.

In the interim, clinicians should consider a lower threshold for germline genetic testing in adolescents presenting with hepatic adenomas, especially in the absence of typical risk factors, or when somatic mutations in DNA repair genes (e.g., ARID1A) are identified in the tumor. This proactive approach could not only inform personalized surveillance strategies but also facilitate cascade screening for at-risk family members, potentially preventing future cancer diagnoses. For an in-depth understanding of hepatic pathologies, including those discussed here and their broader implications, readers may consult Sherlock's Diseases of the Liver and Biliary System.

CLINICAL IMPLICATIONS

A germline ATM mutation demands genetic counseling. The patient and family members face an increased risk of other cancers. This changes everything. Surveillance strategies may need more frequent imaging and screening for other malignancies.

A DNA repair deficiency can influence HCC treatment decisions. But specific therapies in ATM-mutated HCC lack robust efficacy data. A cautious approach is necessary.

This adds complexity to the diagnostic pathway. Hospitals require new protocols. They must triage young HCA patients for genetic evaluation and integrate findings into multidisciplinary plans. Expect insurer resistance. Genetic testing coverage may be an uphill battle without strong evidence. Clinicians will need to fight for it.

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