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Editorial

Hepatocellular adenoma in type Ia glycogen storage disease

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Hepatic adenomas treated with percutaneous ethanol injection in a patient with glycogen storage disease type Ia

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Glucose-6-phosphatase deficiency results in a variety of metabolic disturbances, which lead to well described clinical states that include hepatomegaly, hypoglycemic episodes, short stature, lactic acidemia, and growth retardation. Focal hepatic lesions, including hepatocellular adenoma (HCA), develop quite frequently during the course of this disease. HCAs are also known to develop in most patients with type Ia glycogen storage disease (GSD) by the time they reach their second or third decade of life.[1–3] The overall prevalence of adenomas in the patients with type Ia GSD reported so far in the literature may be close to 50%.[1–8] The natural course of HCA occurring in type Ia GSD liver has recently been made clear. The life-threatening factors in this tumor are twofold: malignant transformation and intratumoral bleeding. However, the pathogenesis of HCA and its real potential to transform into hepatocellular carcinoma (HCC) still remain controversial.

It is well accepted that HCC often develops at the time that adenoma occurs in type Ia GSD patients. In such patients, HCCs have been diagnosed either at autopsy or at an advanced stage of malignancy.[4–7] In one series, in 49 reported cases of patients with type Ia GSD bearing HCA somewhere in the liver, there were at least 9 patients with 9 HCC (18%), the youngest patient being 6 years old at the time of the diagnosis of cancer.[5] However, in another series, no HCC was observed in 43 GSD patients bearing HCA.[9] In Japan, 13 cases of HCC have, so far, bean reported to be associated with type Ia GSD.[10,11] From these reports, it is clear that livers bearing HCA in patients with type Ia GSD are at risk of developing HCC, regardless of whether the HCC results from an adenoma-carcinoma sequence or de-novo carcinogenesis.

It has been suggested that there is an adenoma-carcinoma sequence in HCCs associated with type Ia GSD. After the first report of HCC association in a patient with type Ia GSD, by Zangeneh et al.[6] in 1969, HCA in a 3-year-old patient was reported to have developed into HCC when the patient was 23 years of age.[12] Gordon et al.[13] also reported a case of HCC localized in the same area as an HCA lesion identified 5 years previously. Coire et al.[3] reported that 4 of 36 HCAs (11%) transformed into HCCs. To date, a total of ten HCA patients are reported to have developed HCC.[10,14] Based on these reports, it appears that HCA occurring in type Ia GSD is at risk of malignant transformation. In addition, the fact that HCC has never been reported in the absence of preexisting or coexisting adenoma[1,3–7] makes such an adenoma-carcinoma sequence theory seem logically probable. Furthermore, Limmer et al.[2] reported an HCC developing in a pateint with type Ia GSD; the histology showed an area of the HCC intimately contained within an otherwise unremarkable adenoma, suggesting HCC occurrence within HCA. This observation also strongly supports the idea of an adenoma-carcinoma sequence in HCA associated with type Ia GSD.

However, this adenoma-carcinoma sequence remains controversial, because accurate proof of malignant transformation may be extremely difficult to obtain, as adenomas are usually numerous and scattered throughout the liver, especially in the type of HCAs associated with GSD. In addition, in spite of the recent advances in imaging technologies, differentiation between HCA and HCC is almost impossible, because the radiological features of HCA completely mimic those of HCC, even on computed tomographic angiography or magnetic resonance imaging. Moreover, even histopathological studies sometimes fail to reach a definitive diagnosis of HCA, which is often misdiagnosed as well differentiated HCC, or vice versa, from biopsy samples. It has been reported that even histopathological examination of explanted liver removed at transplantation missed the diagnosis of HCA.[15] For these reasons, some hepatologists and pathologists doubt the theory that

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adenoma develops to HCC. They speculate that such lesions may have originally been well differentiated HCC, and were simply misdiagnosed as adenoma, while the subsequent dedifferentiation appeared to be like a malignant transformation.[16] More detailed studies, especially pathological studies of explanted liver, are needed to solve this question in the future.

There is a well recognized association of HCA with the use of oral contraceptives or the long-term use of androgenic steroids.[17] This type of HCA is usually single, large, and encapsulated, as opposed to the HCA observed in type Ia GSD, which is usually multiple, smaller, and nonencapsulated. In addition, these HCAs usually regress after cessation of hormone intake, whereas in HCA in type Ia GSD, regression is not observed.[3] These findings suggest that HCA in patients with type Ia GSD is more likely to arise secondary to their metabolic abnormalities, rather than being associated with hormonal imbalance.[3] For these reasons, therapeutic strategies may differ for HCAs occurring in GSD and those associated with hormonal imbalance.

To date, in regard to the management of HCA, resection has been the first choice of treatment if the number of nodules is relatively small, because the nodules have a high risk of "malignant transformation" or severe intratumoral hemorrhage. However, liver transplantation may be a better choice of treatment than resection in patients with type Ia GSD when dietary treatment fails or when HCAs develop, because the multicentric occurrence of HCAs and HCCs is then likely. Transplantation also normalizes glucose metabolism, serum lipid levels, and growth retardation, resulting in good quality of life, although the long-term outcome of transplantation in large patient populations is not yet fully established.[8]

In the management of relatively large HCAs, percutaneous ethanol injection therapy (PEIT), however, is extremely efficient, as described in this issue of the *Journal*.[18] Transcatheter arterial embolization (TAE) has also been reported to be effective for the management of HCA.[19,20] Therefore, in addition to TAE, PEIT would be another choice of treatment if resection is not indicated because of multiple HCAs, or if the patient needs treatment while on a waiting list before liver transplantation.

Based on these considerations, both PEIT and TAE may be favorable alternatives to surgery, not only for HCC but also for HCA, when multiple HCAs are seen in type Ia GSD. Such minimally invasive treatments should be considered before transplantation, especially in countries like Japan, where liver transplantation from brain-dead donors is difficult to perform in practice in a routine clinical setting.

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