

Liver lesions in children post-oncologic therapy: Review of case reports and institutional observation

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Received January 05, 2015; Revised February 15, 2015; Accepted February 16, 2015; Published Online February 20, 2015

Original Article

Abstract

Purpose: Focal nodular hyperplasia (FNH), a benign hepatic tumor with ill-defined etiology, has been increasingly reported in children treated for extra-hepatic malignancies. Serial imaging or biopsy may be needed when survivors present with liver lesions. This study aims to review the literature, compare them with our institution's cohort and propose a less invasive diagnostic imaging modality for FNH utilizing Magnetic resonance imaging (MRI) with gadoxetate disodium. **Methods:** We reviewed 13 case reports/series published over the last 20 years and compared them to our retrospective review of 16 childhood cancer survivors (CCS) found to have liver lesions on various imaging studies. Several patients underwent biopsy for diagnosis. **Results:** No specific generalizations could be made in terms of which specific chemotherapeutic agents cause FNH. Seven out of 11 patients underwent radiotherapy and/or hematopoietic stem cell transplant. Additionally, 36% (4/11) had been treated for neuroblastoma. From the literature review, the use of MRI with gadoxetate disodium was difficult to evaluate. Imaging was mainly accomplished using ultrasound, computerized tomography and MRI with gadolinium. The results were often indeterminate and resulted in biopsy in 6 cases in our institution. In contrast, 5 patients underwent initial MRI with gadoxetate disodium, which confirmed the diagnosis of FNH. **Conclusion:** CCS have an increased risk of developing liver lesions. Consistent with previously published literature, patients exposed to radiotherapy or cytoreductive agents used for hematopoietic stem cell transplants appeared to be at higher risk. A significant proportion (36%, 4/11) of our patients with FNH was previously treated for neuroblastoma. With the introduction of MRI with gadoxetate disodium, imaging may be a viable alternative to biopsy.

Keywords: Hepatic Focal Nodular Hyperplasia; Chemotherapy; MRI with Gadoxetate Disodium; Childhood Cancer Survivors

Introduction

Focal nodular hyperplasia (FNH) is a benign hepatic tumor of epithelial origin and is the most common benign non-vascular tumor of the liver.¹ Its incidence is second only to hepatic hemangioma, which is the most common benign liver tumor of infancy. The classic population affected by FNH is middle-aged females; the condition is rare in pediatric populations.^{1, 2} However, increases in the frequency of routine imaging studies such as abdominal ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) scans have resulted in an increased identification of these lesions, often considered an incidental finding. Hepatic FNH may be associated with vague abdominal symptoms or elevation in liver enzymes, but they are usually found without other corollary abnormalities.³

Although the etiology of FNH is unknown, a relationship to oral contraceptive (OCP) use and vascular abnormalities has been suggested.² History of cytoreductive chemotherapy

including busulfan and melphalan total body irradiation and high dose chemotherapy have also been proposed as possible risk factors as FNH has been seen at increased frequency in long-term survivors of childhood malignancies.⁴ In particular, chemotherapies such as cyclophosphamide and dactinomycin that induce hepatic vascular endothelial injury or veno-occlusive disease appear to increase the risk of developing FNH as a delayed complication.⁵

These chemotherapeutic agents are often used in the treatment of pediatric solid tumors such as germ cell tumor, Wilms'tumor, sarcomas and neuroblastoma. One study placed the incidence of FNH in post-chemotherapy pediatric patients at 5.1% (versus 0.045% in the general pediatric population).⁵ Certain malignancies appear to confer a higher risk of developing FNH than others, including medulloblastoma, malignancies treated with hematopoietic stem cell transplant and notably, neuroblastoma.^{2, 4, 6} One study placed the inci-

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Cite this article as: Gologorsky R, Wong V, Holmes W, Haider A, Imagawa D, Torno L. Liver lesions in children post-oncologic therapy: Review of case reports and institutional observation. *Int J Cancer Ther Oncol* 2015; 3(2):03027. DOI: 10.14319/ijcto.0302.7

dence of FNH in pediatric patients post-hematopoietic stem cell transplant as high as 12% (17/138).¹ However, few authors have explored the development of FNH in the context of specific oncologic therapy in this patient population.

Diagnosis of hepatic FNH is based on radiographic imaging, with confirmatory biopsy when necessary. Lesions may be single or multiple and may vary in size. Significantly, it has been noted that FNH in children post-oncologic therapy have a higher incidence of atypical features on imaging including multiple lesions and lack of the classic central scar.⁷ Histological findings on biopsy specimens include a nodule composed of benign-appearing hepatocytes. Typically, hepatic FNH lesions have large arterial supplies and fibrous stroma that form prominent stellate scars.⁸ Diagnosticians must differentiate these lesions from metastatic liver lesions or de novo hepatocellular carcinoma (HCC).

Here, we review the literature on pediatric focal nodular hyperplasia. We also sought to compare findings from our cohort of long-term cancer survivors with hepatic focal nodular hyperplasia against data from published literature. We postulate a mechanism that may augment our understanding of liver FNH etiology as there is scarcity of knowledge on this topic in the literature. Our paper will not alter currently recommended follow-up care of patients with FNH lesions. However, it is hoped that it will help advance knowledge of FNH pathogenesis as a possible iatrogenic effect of cancer therapy. In addition, we report our institution's experience with a hepatocyte-specific MRI agent, gadoxetate disodium, as an alternative option to biopsy in differentiating FNH from other lesions.

Methods and Materials

We conducted a review of case reports/series published over the last twenty years (N = 75 pediatric patients with FNH) and did a retrospective analysis of long term survivors of pediatric cancers found to have liver nodules from our institution's database (N = 16).

Out of the sixteen patients who were evaluated in our institution between 2001 and 2013, eleven patients (11/16) with hepatic FNH were identified. Demographic and clinical data were abstracted from each patient's medical records, including malignancy diagnosis, age at diagnosis, type of therapy used, duration of therapy, co-morbid conditions and duration of time between end of treatment and diagnosis of liver lesions. Imaging studies, including ultrasound, computerized tomography, and magnetic resonance imaging with gadolinium were reviewed by our board-certified pediatric radiologist. Of the eleven patients with FNH, six underwent biopsy for further characterization of their lesions.

The biopsies were performed prior to our institution's use of gadoxetate disodium. Eventually, all eleven patients underwent imaging using gadoxetate disodium which confirmed FNH. Follow-up analysis was determined on a case-by-case basis but typically included repeat imaging after 3 months (N = 8 out of 16) and liver function tests. Data from our patients and from those published in the literature were compiled and analyzed for trends.

Clinical characteristics of the patients are summarized in **Table 1**.

TABLE 1: CCS found to have liver lesions from our institutional cohort.

Pt	Sex	Diagnosis	Adjuvant therapy	Interval (yrs)	Imaging	# of lesions	Biopsy	FNH
1	F	PNET	XRT/BMT	13	US, CT, MRI-G	multiple	n/a	No
2	M	Langerhans Cell Histiocytosis	XRT	5.6	US, CT, MRI-G	3	n/a	No
3	M	Neuroblastoma, IV	XRT/BMT	7.9	US, CT, MRI-G	3	Yes	Yes
4	M	Germ Cell Tumor	None	13.5	US, MRI-G	1	No	No
5	F	Neuroblastoma, III	TBI/BMT	9	US, CT, MRI-G	6	Yes	Yes
6	M	Neuroblastoma, IV	XRT/BMT	1.3	US, CT	3	No	Yes
7	F	Germ Cell Tumor	None	10.5	US, MRI-E	1	No	Yes
8	M	Congenital Medulloblastoma	XRT/BMT	6.6	US, CT, MRI-G,	multiple	Yes	Yes
9	F	Neuroblastoma, IV	XRT/BMT	4.6	US, CT	1	Yes	Yes
10	F	ALL	None	2.3	PET/CT, MRI-G	multiple	Yes	No
11	M	Wilms Tumor, III	None	4.3	US, CT, MRI-G	1	Yes	No
12	F	PNET	XRT/BMT	10	CT	1	No	Yes
13	F	Ewing's sarcoma	XRT	.6	CT, MRI-E	multiple	No	Yes
14	F	Germ Cell Tumor	None	0	CT, MRI-E	1	No	Yes
15	F	Hepatoblastoma, IV	Liver transplant	.25	MRI-E	1	No	Yes
16	F	Rhabdomyosarcoma	None	6	MRI-E	1	No	Yes

MRI-G = MRI-Gadolinium; MRI-E = MRI-Gadoxetate disodium; Interval years = Time from end of treatment to diagnosis of liver lesions.

TABLE 2: Therapeutic exposures of patients who developed FNH.

Patient	Sex	Diagnosis	Chemotherapy	BMT Prep. Regimen	XRT Site	VOD
3	M	Neuroblastoma Stage IV	VCR/CPM/Doxorubicin Cis-Retinoic acid Chimeric 14.18/Interleukin2	Carboplatin Etoposide	Retroperito- neum	N
5	F	Neuroblastoma Stage III	VCR/Adriamycin/CPM Cisplatin/Etoposide Topotecan Anti-Idiotypic Vaccine Cis-Retinoic acid	Carboplatin Melphalan Etoposide	MIBG therapy TBI	N
6	M	Neuroblastoma Stage IV	VCR/Etoposide/Doxorubicin CPM/Cisplatin	Carboplatin Etoposide	Retroperito- neum	N
7	F	Germ cell Tumor	Cisplatin/Etoposide Bleomycin	N	N	N
8	M	Congenital Medulloblastoma	Carboplatin/ Cisplatin/ CPM Etoposide/Temozolomide VCR	Thiotepa	Cranial	N
9	F	Neuroblastoma Stage IV	VCR/Etoposide/Doxorubicin CPM/Cisplatin	Carboplatin Etoposide	TBI	N
12	F	PNET	VCR/Doxorubicin/CPM Ifosfamide/Etoposide Carboplatin	CPM Etoposide	Cranial	N
13	F	Ewing's Sarcoma	VCR/Doxorubicin CPM/Ifosfamide Etoposide/Carboplatin	N	Y	N
14	F	Germ Cell Tumor	Cisplatin/Etoposide Bleomycin	N	N	N
15	F	Hepatoblastoma	5FU/VCR/Cisplatin	N	N	N
16	F	Rhabdomyosarcoma	VCR/Dactinomycin/CPM	N	Y	N

VCR = Vincristine; CPM = Cyclophosphamide; MIBG = Iodine-131 meta-iodo-benzylguanidine; TBI = Total body irradiation; PNET = Primitive neuroectodermal tumor; 5 FU = Fluorouracil

Results

Summary of Observations

A review of our institution's cohort and case series/reports published in the literature within the last 20 years, identified 75 total patients with hepatic FNH (34 boys and 41 girls; mean age at initial cancer diagnosis 5.7 years; mean number of years between diagnosis of primary malignancy OR bone marrow transplant and diagnosis of FNH, approximately 8.75 years). Of the 75 total patients we analyzed with FNH, 64 patients (64/75) were found on literature review. Analysis of our institution's database of pediatric cancer long-term survivors yielded sixteen patients with liver lesions. Eleven of these patients were diagnosed with FNH.

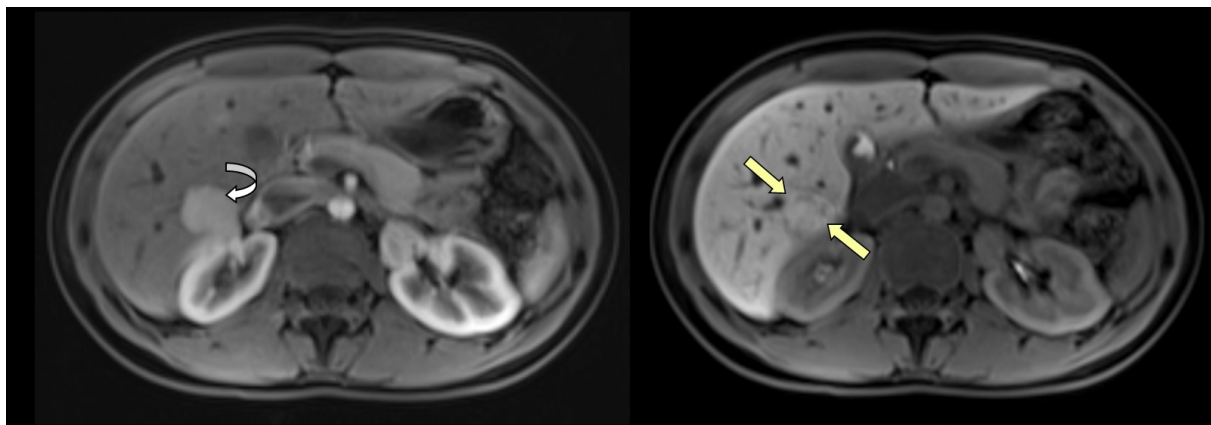


FIG. 1: 14 year old female with rhabdomyosarcoma of cervix. Hypodense right lobe liver lesion found on surveillance CT (not shown). Left image shows axial MRI of the abdomen, T1 arterial phase after administration of gadoxetate disodium. (curved arrow) Enhancing mass segment 6 of the liver. Right image shows axial MRI abdomen. T1 hepatobiliary phase, 20 minute delay after gadoxetate disodium administration. (yellow arrows) The mass retains enhancement equal to or slightly greater than background liver. Findings are consistent with FNH.

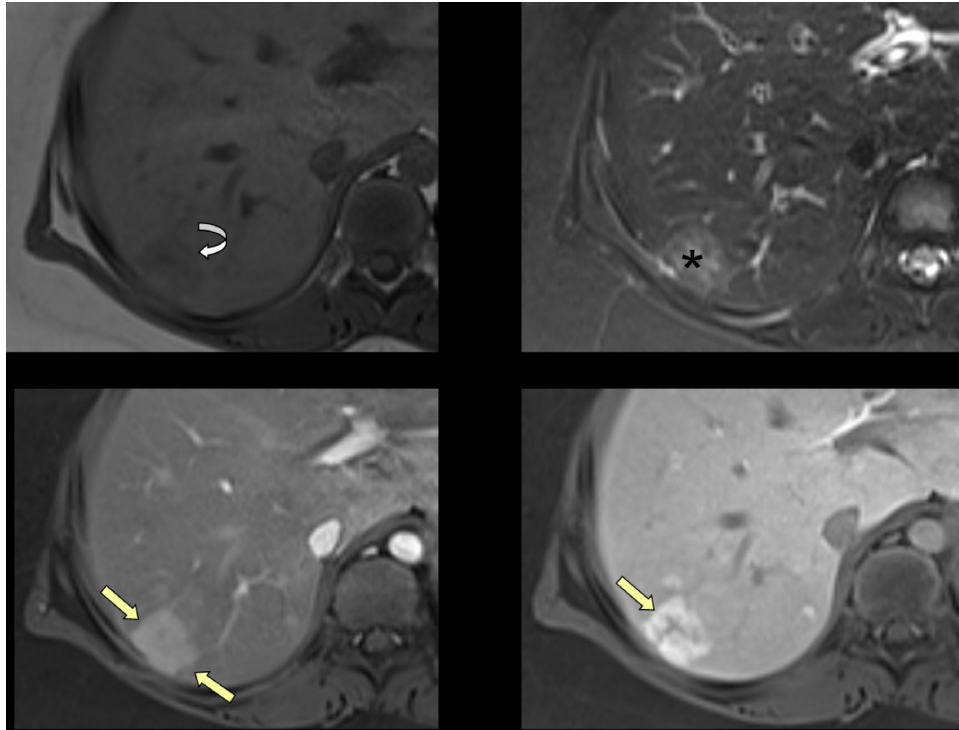


FIG. 2: 10 year old male with medulloblastoma. MRI of lumbar spine for surveillance showed right lobe liver lesion. Upper left image shows axial MRI of the abdomen, T1 pre contrast. (curved arrow) Slightly T1 hypointense mass segment 7 of the liver. Upper right image shows axial MRI abdomen T2 fat sat pre contrast. (asterisk) The mass is slightly T2 hyperintense compared to liver background. Left lower image shows T1 arterial phase after gadoxetate disodium. (yellow arrows) Mass shows enhancement. Right lower image shows T1 sequence hepatobiliary phase, 20 minute delay after gadoxetate disodium administration. (yellow arrow) The mass retains enhancement greater than background liver. Findings are consistent with FNH. Note central scar.

In more detail, in our cohort, 12/16 patients underwent MRI following discovery of hepatic lesions on US or CT. Of these 12 patients, 7 had MRI with gadolinium and 5 had initial MRI with gadoxetate disodium. **Figures 1 and 2** show representative images of FNH noted after gadoxetate disodium at our institution. Among patients who were imaged using gadolinium, 5 required biopsy due to indeterminate findings whereas none of those who initially received gadoxetate disodium had to be biopsied because of diagnostic findings. The results of the biopsies showed benign regenerative tissue (3), benign fatty liver (1), spindle cell neoplasm (1) and 1 was indeterminate. None of those who were initially imaged with gadoxetate disodium had to be biopsied because of highly characteristic findings using gadoxetate disodium. Patient 9 underwent biopsy after CT imaging alone based on the treating physician's decision. Patient 8 underwent biopsy after gadolinium imaging due to inconclusive results. This occurred prior to our institutional use of gadoxetate disodium contrast. Pathology showed benign fatty liver. He subsequently underwent MRI with gadoxetate disodium once the contrast became available at our institution, and this revealed characteristic findings of FNH.

Consistent with previously published literature, a significant proportion of our patient population had been treated for neuroblastoma (4/11). These patients received cisplatin,

etoposide, cyclophosphamide, doxorubicin and carboplatin, which are agents commonly used for solid tumors. None developed veno-occlusive disease during treatment. Seven out of eleven patients underwent radiotherapy and/or hematopoietic stem cell transplant. Just over half (6/11) of our patients had multiple foci of FNH. No significant generalizations could be made in terms of specific causative chemotherapy agents, history of veno-occlusive disease or the presence or absence of graft versus host disease. Imaging techniques used at outside institutions could not be evaluated due to insufficient reporting.

Discussion

Hepatic FNH lesions are considered a result of a hyperplastic rather than a neoplastic process. Classically, FNH forms a nodular lesion characterized by a central stellate scar with malformed vascular structures and thickened hepatic plates that form radiating fibrous septa (**Figures 1 & 2**).⁹ These changes have a characteristic radiologic appearance by MRI with gadoxetate disodium. In a study examining 305 confirmed cases of FNH, Nguyen *et al.* reported that FNH lesions were well-limited from the surrounding liver, implying a regional rather than a global hepatic insult.¹⁰ Lough *et al.* presented indirect evidence of regional circulatory disturbances and proposed that thrombosis might result in vascular

narrowing leading to FNH.¹¹ Additionally, Kumagai *et al.* showed direct evidence of arterial and portal thrombi and recanalization of arteries in a nodule.¹² They postulated that hepatic arterial recanalization and tissue perfusion following a thrombotic ischemic event results in changes consistent with the radiologic stellate appearance.¹² The stellate scar is likely the end-stage of progressive sclerosis or thrombosis of vascular malformation.¹³

Results from earlier studies emphasized the high prevalence of neuroblastoma and germ cell tumors among patients diagnosed with FNH.² This was similarly shown in our patient cohort. Majority of these children are treated with varying combinations of high dose chemotherapy, however, the occurrence of FNH may be linked to the nature and intensity of the treatment rather than the histologic diagnosis.

Ruling out malignant hepatic lesions is particularly important in patients previously treated for malignancy. Historically, diagnosis has relied on imaging studies that utilize radiation, such as CT, and/or invasive techniques such as biopsy. The elevated incidence of FNH with atypical features, especially lack of central scar and multiplicity, emphasizes the need for ideal diagnostic imaging methods.

Fortunately, recent advancements in imaging technology have yielded greater accuracy when diagnosing with imaging alone. Ultrasound, CT, as well as MRI with traditional extracellular gadolinium agents each have limitations in differentiating FNH (a benign lesion) from other hepatic lesions that require treatment. Ultrasound features of FNH are not specific and do not allow differentiation from other hepatic lesions.¹⁴ On dynamic contrast-enhanced CT, FNH exhibits isoattenuation on precontrast phase, hyperattenuation during the arterial phase, and isoattenuation on the portal venous phase. This pattern is referred to as a “stealth” appearance, as enhancement is only seen on the arterial phase and, on pre-contrast images, the lesion blends into background liver attenuation. A portion of these lesions demonstrates a central scar but this is also seen in hepatic adenoma, fibrolamellar hepatocellular carcinoma, giant hemangiomas, and others. Despite the superior soft tissue contrast of MRI as compared to CT, MR signal patterns of FNH and central scar are unreliable and may appear atypical, ultimately requiring biopsy for a definitive diagnosis.¹⁵

Because FNH is essentially a localized abnormal arrangement of functioning hepatocytes with some biliary elements that do not connect to the biliary tree, hepatocyte-specific gadolinium agents have improved the accuracy of diagnosing FNH. One such agent, gadobenate dimeglumine, Gd-BOPTA, (Multihance, Bracco Imaging, Milan Italy) was FDA approved in 2004 and has up to 4% hepatocyte uptake and excretion into the biliary system. Because of the structure of FNH mentioned above, the hepatocyte-specific agent has delayed clearance. On delayed images, FNH is hyperintense or iso-

intense at 1-2 hours to background liver.¹⁶ Non-FNH lesions are hypointense to background liver. Since 2008, another hepatocyte-specific MRI agent, gadoxetate disodium (Bayer Health-Care) has been FDA approved and has been used for the diagnosis of FNH.¹⁷ Gadoxetate disodium is transported into hepatocytes via enterohepatic circulation and is eliminated equally by biliary and renal excretion. Due to the high level of uptake by hepatocyte and relatively weak binding to extracellular proteins, hepatocytes will be greatly enhanced on a T1-weighted image. Gadoxetate disodium also has a high level of relaxivity, which results in proportional increased enhancement on T1 weighted image. This allows for gadoxetate disodium to be dosed at one-quarter the volume (0.025 mmol/kg body weight) of other gadolinium-based contrast agents.¹⁷ Compared to gadobenate dimeglumine (Gd-BOPTA), gadoxetate disodium only requires 20 min of delayed imaging to reach the hepatocyte phase. MRI with gadoxetate disodium now nearly obviates the need for histologic confirmation of FNH, especially when characteristic features of hepatic FNH are found in patients with low risk factors for HCC.¹⁸ Gadoxetate disodium, which is taken up only by functioning hepatocytes, is the contrast agent that produces the greatest specificity.¹⁹ Importantly, gadoxetate disodium also enables physicians to distinguish between FNH and other liver lesions- including adenoma, HCC, and dysplastic nodules- at a high level of accuracy.¹⁸ Other recent studies comparing MRI with gadoxetate disodium to contrast-enhanced CT for the differentiation of incidentally-found benign versus malignant hepatic lesions have concluded that MRI with gadoxetate disodium yields higher accuracy of diagnosis versus CT.⁹ Authors additionally determined that MRI with gadoxetate disodium is superior for the radiologic diagnosis of FNH.²⁰ The sensitivity and specificity of using MRI in healthy children with suspected FNH is 82.6% and 97.4%, respectively.²¹

Our institutional experience reflects the above findings. Of the five patients who underwent initial MRI with gadoxetate disodium, none underwent biopsy. Given this data, an evolving trend towards the use of hepatocyte-specific contrast imaging is emerging as a major diagnostic criterion for FNH. At this time, it may appear reasonable to suggest imaging using hepatocyte-specific agents and clinical picture alone to diagnose and follow FNH. Furthermore, the use of imaging with hepatocyte-specific agents may altogether obviate the need for invasive or irradiating techniques in the work-up of FNH. Once diagnosed, most lesions do not require treatment unless patients are clearly symptomatic, or lesions significantly increase in size or if radiological investigations show signs of intralesional hemorrhage.²²

Conclusion

FNH is an uncommon benign hepatic tumor that is most commonly detected incidentally. Recently, this condition has been described in increasing frequency among childhood

cancer survivors. It is important for clinicians to be aware of this clinical entity as survivors transition into adulthood. When found in children previously treated for extra-hepatic malignancies, the need to rule out metastasis is particularly important. Diagnosis has historically been made using CT and biopsy. However, with higher accuracy imaging with MRI with gadoxetate disodium, clinicians now have a viable non-invasive option to diagnose FNH in this patient population. Since FNH rarely causes complications, conservative management with serial imaging and assessment of liver function is recommended. In the event of enlargement or occurrence of symptoms, resection is usually advised.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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