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Hepatic Adenoma Secondary to Long-Term Oral Contraception Use in a Young Female

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Abstract

Hepatic adenomas are a rare byproduct of oral contraceptive pill (OCP) use. Laboratory workup is often inconclusive. Diagnosis can be made via MRI; however, select cases may require further testing such as fine needle aspiration or core needle biopsy. We report a case of a 36-year-old female who was referred to gastroenterology for further evaluation of several liver lesions found incidentally on imaging. Due to risk factors, such as age, long-term oral contraceptive use and obesity, adenoma was high on the differential. Although infrequent, this case emphasizes the importance of a detailed history, including medication review, and physical examination.

Keywords

Hepatic Adenoma, Oral Contraceptives, Liver Lesion

1. Introduction

Hepatic adenomas, also called hepatocellular adenomas (HCA), are rare, accounting for approximately 1 - 1.3 per million in non-OCP users and 30 - 40 per 100,000 in long-term OCP users [1]. A retrospective case-control study performed by the Centers for Disease Control (CDC) and Armed Forces Institute of Pathology (AFIP) demonstrated a direct correlation between the duration of OCP use and the formation of hepatocellular adenomas. There was also found to be an increased risk of HCA formation with the use of high potency OCPs [2]. Concomitantly, prior to the introduction of OCPs to medicine in the 1960s, the incidence of HCAs was almost null, leading scientists to further strengthen this connection [3]. Other causes of HCA include anabolic androgen use, genetic

syndromes, and obesity and metabolic syndromes [1].

Typically, hepatic adenomas are found incidentally on imaging and are mostly seen in women of reproductive age who have a history of OCP use [4]. When patients are symptomatic, they most often describe episodic abdominal pain that is localized to the epigastrium or right upper quadrant [5]. This episodic pain could represent a complication such as bleeding into the hematoma, an enlarged liver (hepatomegaly), or necrosis.

Physical examination may or may not show an abdominal mass and jaundice is rare [6]. Labs including liver biochemical and function testing are typically unremarkable but patients with large adenomas may have an elevation in alkaline phosphatase or gamma-glutamyl transpeptidase (GGT). Serum biomarkers of inflammation may be elevated in some subclasses of HCA's, such as inflammatory HCAs [7]. For imaging, HCAs tend to be well visualized on CT and MRI, demonstrating a well-demarcated lesion [8].

The risk of malignant transformation from HCA to hepatocellular carcinoma is approximately 5% [9]. Risk factors for malignant transformation include beta-catenin activation subtype, male sex, and a lesion size of >5 cm. Hepatocellular adenomas should be monitored for size and increasing size should raise suspicion for malignant transformation. The long-term prognosis for patients with malignancy who receive surgical intervention is good, and often without recurrence [10].

The objective of this case is to highlight the importance of presentation and history when working up hepatic lesions, as well as, emphasizing the alternate diagnostic routes based on presentation, sex and imaging/laboratory findings.

2. Report of Case

A 36-year-old Caucasian female with a past medical history of type 2 diabetes mellitus, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), hypothyroidism, and obesity presented to the gastroenterologist for further evaluation of a liver mass found incidentally on imaging. Surgical history is significant for recent cholecystectomy. Medications include Euthyrox 100 mcg, Metformin 500 mg twice daily, and Sprintec 0.25 mg - 35 mcg tablet. Patient denies family history of liver disease apart from fatty liver in her mother.

Prior to this office visit, the patient had a CT of the abdomen and the pelvis that showed several hypodense masses measuring 1.4 cm and 2 cm in the right hepatic lobe (**Figure 1**). MRI was done for further evaluation and showed multiple enhancing liver lesions measuring up to 2.4 cm with suspicion for possible metastatic disease (**Figure 2**). Ascites was not appreciated. Magnetic resonance cholangiopancreatography (MRCP) was done and was unremarkable. Biopsy was recommended at this time to rule out malignancy, which the patient had scheduled but not yet undergone. At this time, patient reported intermittent abdominal discomfort. She had intentionally lost 45 pounds over the past year through diet and exercise. Physical exam was notable for morbid obesity with a body mass index (BMI) of 42.2. Abdominal exam was significant for diffuse tenderness with palpation but no organomegaly appreciated.

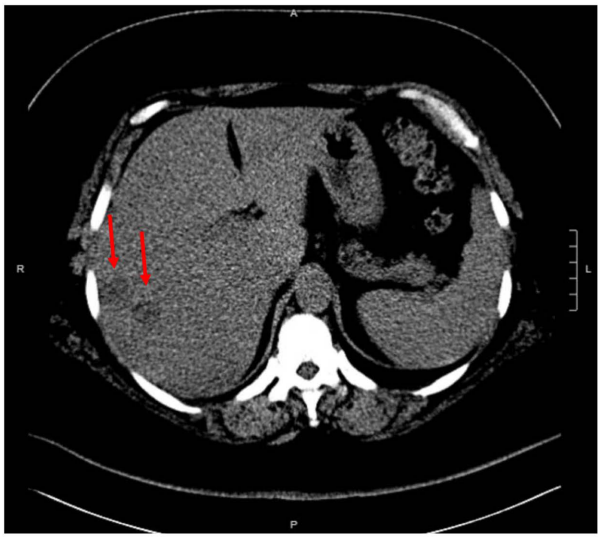

Figure 1. CT abdomen/pelvis showing several hypodense masses measuring 1.4 cm and 2 cm in the right hepatic lobe (red arrows).

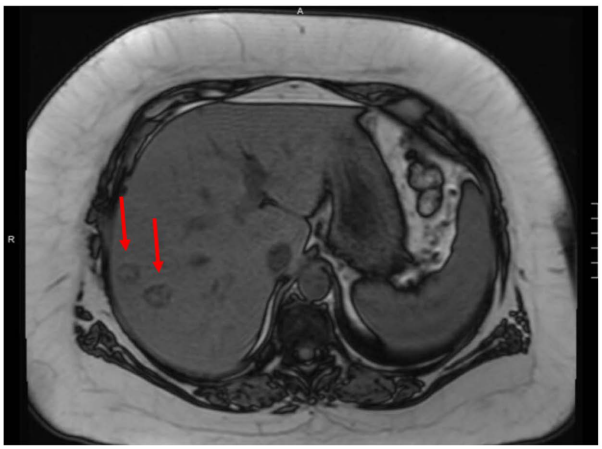

Figure 2. MRI showing multiple hepatic nodules measuring up to 2.4 cm (red arrows). Nature is indeterminate; however, hepatic adenomas is a differential consideration.

Patient returned for follow up several months later. Laboratory workup showed normal gamma-glutamyl transferase (GGT) and alpha-fetoprotein (AFP). Patient had a liver biopsy at an outside facility that showed no evidence of malignancy, per charge review; however, the biopsy sample did not contain a significant amount of liver tissue so repeat biopsy was advised, which the patient agreed to do at a later date. Patient followed up with her gynecologist who discontinued her previous oral contraceptive and started her on Jencycla, which contains only progesterone. Physical examination was unremarkable, and patient noted overall improvement in prior symptoms. Follow up MRI in 6 months was also recommended for surveillance. Patient was agreeable with assessment and plan.

Repeat MRI was obtained and was significant for numerous nodules within the liver measuring up to 2.0 cm with diffuse hepatic steatosis (**Figure 3**). There

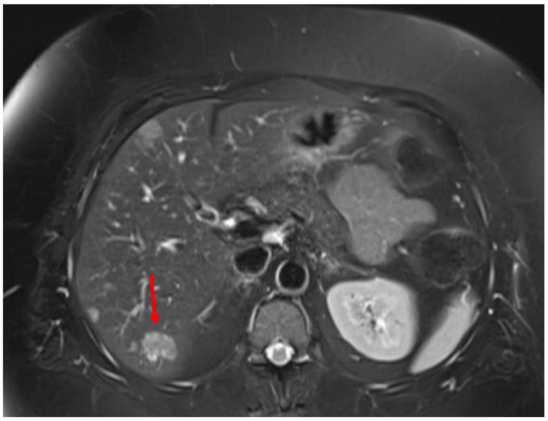

Figure 3. Repeat MRI showing numerous nodules within the liver measuring up to 2.0 cm (red arrow). These demonstrate slight T1 and T2 hyperintensity and slight enhancement. Nature is indeterminate. There is a background of diffuse hepatic steatosis.

was a slight decrease in size as the prior imaging indicated a liver lesion measuring 2.4 cm. This improvement further corroborated our suspicion for hepatic adenoma. The decrease in lesion size was likely a result of changing the patients birth control from Sprintec to Jencycla. She reported no symptoms at this time and repeat biopsy was put on hold as imaging confirmed improvement. Patient is to follow up with GI in 6 months for repeat imaging.

3. Discussion

Hepatic adenomas are rare, benign, solitary liver lesions [11]. Associated risk factors include prolonged estrogen exposure, anabolic androgen use, genetic syndromes such as glycogen storage diseases and familial adenomatous polyposis (FAP), and obesity and/or metabolic syndrome.

Clinically, patients are typically asymptomatic; however, they may describe periodic abdominal discomfort. Laboratory studies, including liver function testing, are generally not helpful in the diagnosis of hepatic adenomas because these laboratory values are usually within normal limits [12]. However, patients with large adenomas may have elevated gamma-glutamyl transpeptidase (GGT) and/or alkaline phosphatase (ALP). Inflammatory markers, such as C-reactive protein (CRP), may also be elevated.

As mentioned previously, most patients with hepatic adenomas are asymptomatic and will present after a solitary liver lesion is found incidentally on imaging such as ultrasound or CT [13]. Beyond the initial imaging, ultrasound will have little diagnostic value as this imaging modality is unable to distinguish between benign and malignant tumors [14]. CT can provide useful information; however, the best modality for imaging hepatic adenomas is MRI with a hepatocyte-specific contrast agent such as gadobenate dimeglumine [15]. On MRI, HCAs are usually well-demarcated because of the fat or glycogen content and will show arterial phase enhancement. The diagnostic approach after MRI differs based on gender, due to the divergence in risk of malignancy between males and females.

For female patients, fine needle aspiration or core needle biopsy is not typically indicated as the risk of malignancy is low and there is often difficulty in microscopically distinguishing adenomas from normal hepatocytes [8]. Several report series conclude that approximately 16% - 20% of adenomas affect men [16]. Small hepatocellular carcinomas are commonly seen more in the male population, and most are associated with an elevated serum alpha-fetoprotein [17]. Thus, in male patients, due to the increased risk of malignant transformation, surgical resection is almost always indicated, and diagnosis is confirmed at that time via histology.

HCAs were once thought to be a single tumor group. However, more recently, it is now understood that HCAs comprise a heterogenous group of liver tumors with a pathology-morpho-molecular correlation. There are several factors that play into the development of hepatocellular adenomas including clinical presentation, etiology, radiologic findings, histopathologic features, and risk of malignant transformation or hemorrhage [18]. HCAs are typically classified based on genotypic and phenotypic features [19]. The HCA subtype can often be determined by viewing arterial phase enhancement patterns on MRI, as the phases vary by lesion type. For example, inactivated HCAs (H-HCAs) typically contain intratumoral fat, whereas, inflammatory HCAs (I-HCAs) characteristically have dilated sinusoids on imaging [20]. If the subtype cannot be determined via MRI, a biopsy with histology can be helpful; however, this is not often carried out in clinical practice. In these different subtypes, genetic mutations can be identified which cause benign, and at times, malignant proliferation of hepatocytes [21]. The HCA subtypes include HCA with hepatocyte nuclear factor 1A (HNF1-1A) alpha mutation, inactivated HCA (H-HCA), inflammatory HCA (I-HCA), and HCA with beta-catenin activation (b-HCA) [4], which are summarized in **Table 1**. HCA with HNF-1A mutations occur almost exclusively in women and are characterized by diffuse steatosis without cytologic abnormalities or inflammatory infiltrates. HNF-1A is a gene that plays an important role in the regulation of glycolipid metabolism and is found mainly in pancreatic beta cells, the intestine, and the liver [27]. On MRI, they demonstrate moderate arterial enhancement that does not extend into the portal venous phase. Similarly, inflammatory HCAs are mostly seen in women. They are characterized by inflammatory infiltrates, tortuous blood vessels, hemorrhage, and sinusoidal dilation. MRI shows intense arterial enhancement that persists into the portal venous and delayed phases. HCA with beta-catenin activation is the least common subtype and is more frequently found in males. They are associated with use of androgens and exhibit no specific characteristics on MRI. Histologically, they have cellular atypia, cholestasis, and pseudoglandular formation. The exon 3 mutation in beta catenin plays a significant role in increasing the risk for malignant transformation [9] [28]. This subtype is rare but explains why prompt surgical intervention with resection is recommended in males with hepatic adenomas due to the higher prevalence in the male population and the increased risk for malignant transformation.

Table 1. MRI findings and clinical features of HCA subtypes.

MRI Sequences and Clinical Features	I-HCA	H-HCA	□-HCA
T_1 weighted imaging	Isointense to mildly hypertense	Isointense to hyperintense	Isointense to hyperintense [22] [23]
T_2 weighted imaging	Markedly T_2 hyperintense Atoll sign: incomplete T_2 hyperintense rim	Isointense to mildly hyperintense	Poorly demarcated T_2-hyperintense scar [23]
Post-contrast imaging	Arterial enhancement that persists on later phases	Variable arterial enhancement that does not persist on later phases	May mimic HCC with arterial enhancement with washout [22] Poorly demarcated scar that enhances in the portal venous phase [23]
Prevalence rate	40% - 50% of cases	30% - 40% of cases	15% - 20% of cases
Risk for malignant transformation	11% [23]	No to low risk [23] [24]	Up to 46% [24]
Hemorrhage	16% - 30% [23] [25]	9% [23] [25]	14% [25]
Management considerations	Conservative management if <5 cm and stable	Conservative management if <5 cm and stable	Resection regardless of size

Management depends on the size and progression of the lesion, patient sex, and if the patient is symptomatic or not [8]. For asymptomatic women with lesions less than 5 cm, conservative management is recommended with observation and follow up with a repeat MRI in six months [28]. The patient should also stop oral contraceptive pill use. If the lesion does not increase in size within that time, patients can follow up with annual MRI surveillance. While the optimal amount of time for surveillance has not been fully established, some authors suggest that surveillance should be continued until menopause [29]. If the lesion appears to be growing or is over 5 cm, surgical intervention is performed as there is risk of hemorrhage with larger lesions. For women who present with symptoms secondary to the lesions, such as persistent right upper quadrant abdominal pain, surgical resection with limited margins is recommended. There are several options for women who are not surgical candidates or who elect to not undergo surgical resection. These options include radiofrequency ablation, transarterial embolization (TAE), and/or observation and surveillance. Transarterial embolization is also recommended for tumors that are complicated by hemorrhage at diagnosis [30]. Surgical resection is always indicated for men with hepatic adenomas irrespective of lesion size due to the associated risk of progression to hepatocellular carcinoma. In general, patients with hepatic adenomas > 5 cm, unclassified or telangiectatic subtypes, and men are at higher risk of complicated disease; therefore, surgical resection should be restricted to these cases [5]. An overview of HCA management is summarized in **Figure 4**.

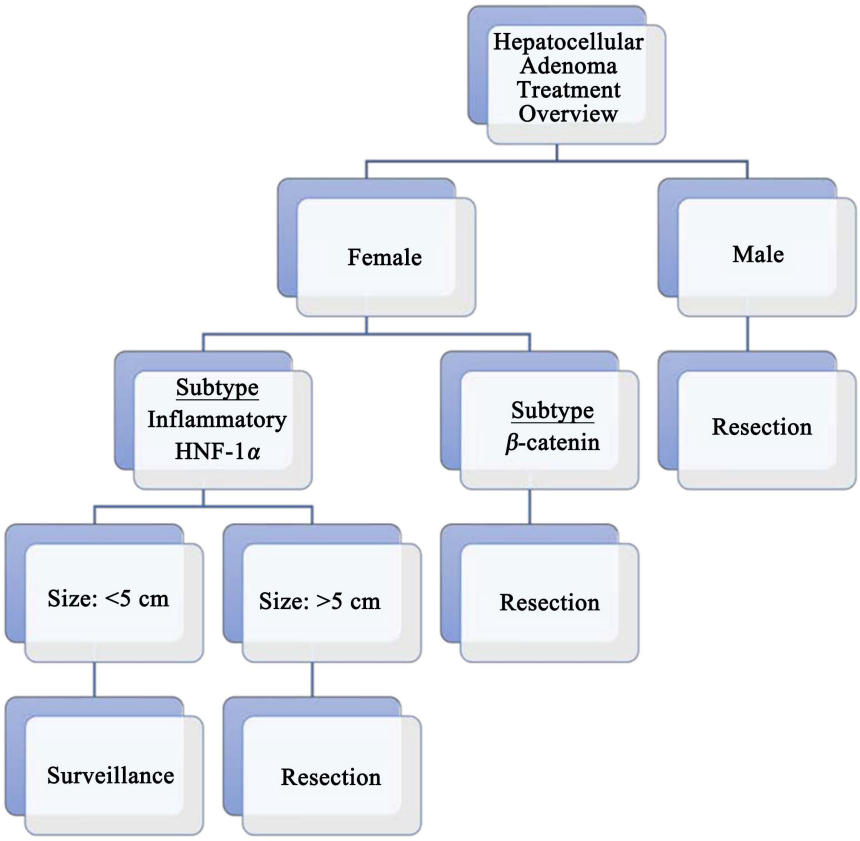

Figure 4. Overview of HCA treatment.

While complications can be uncommon in hepatic adenomas, there are associated complications such as intralesional bleeding, malignant transformation, pregnancy, and liver adenomatosis [10]. The number of lesions does not seem to have an association with risk of hemorrhage, whereas, size of the lesion does [31]. In addition to increased risk of complications secondary to size of tumor, other risk factors include exophytic growth of the tumor and location in the left hepatic lobe [32]. A female patient on OCPs with adenoma(s) may be advised to discontinue birth control putting her at increased risk of pregnancy. On the other hand, pregnancy increases the patient's exposure to hormones which is a known risk factor for increased growth of HCA. Although these complications are uncommon, management with surgical resection should be considered on a case-to-case basis.

4. Conclusion

We present a case describing hepatic adenomas secondary to long-term oral contraceptive use. This case presentation highlights the importance of considering this in the differential diagnosis for female patients with liver lesions found incidentally on imaging. Workup, surveillance, and treatment are dependent on a multitude of factors such as presenting symptoms, size of the lesion, sex of patient, and imaging results.

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None reported.

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None reported.

Author Contributions

Kelsey Lamb and Jessica Darden both contributed to collecting and analyzing supporting research, paper writing and revision, and figure formatting. Suresh Jayatilaka, MD served as supervisor. 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.

Statement

Informed consent was obtained for this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding to the publishing of this article.

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