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Case Report

Hyperandrogenism and malignant degeneration of hepatic adenomas in the setting of Abernethy malformation ☆,☆☆

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ABSTRACT

Abernethy malformation refer to a congenital absence of intrahepatic portal veins leading to a primarily extrahepatic congenital portosystemic shunt. The lack of intrahepatic portal veins leads to a characteristic set of physical exam and imaging findings that may include hyperandrogenism and liver masses such as hepatic adenomas or focal nodular hyperplasia. In this case report, we describe a 20-year-old female who presented with an enlarging hepatic adenoma. A separate hepatic adenoma had previously been biopsied and noted to have undergone malignant degeneration into hepatocellular carcinoma. For each lesion, she was treated with combination transarterial embolization and microwave ablation. On follow-up imaging after therapy, it was then noted that her extrahepatic portal vein drained directly into the inferior vena cava, consistent with congenital portosystemic shunt. Recognition of this vascular anomaly is critical in treatment planning, as early intervention with either medical therapy or surgery can prevent the metabolic sequela of this unique constellation of symptoms.

Introduction

Congenital portosystemic shunt (CPSS), also known as Abernethy malformation, is a rare congenital absence of the portal vein leading to a primarily extrahepatic portosystemic shunt. Persistent shunts from CPSS can lead to chronic reduction in enterohepatic circulation, resulting in variable presentation of metabolic derangements and hepatic neoplasms. We report a patient with a history of unexplained hyperandrogenism, hirsutism and growing adenomas, one of which was previously biopsied and found to have undergone malignant degeneration into hepatocellular carcinoma. Each of her growing liver lesions was treated with combination transarterial therapy and microwave ablation, but then noted on follow-up imaging to have CPSS anatomy. With newfound clarification of the

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etiology of symptoms, the treatment team and patient was able to ultimately pursue a conservative medical management strategy.

Case report

A 20-year-old female with a history of primary amenorrhea due to hyperandrogenism was found to have multiple hepatic adenomas in the setting of a non-cirrhotic liver. Her most recent physical exam revealed absence of breast growth consistent with a Tanner stage 2. Her physical exam was also positive for acne, hirsutism, clitoromegaly, as well as mild acanthosis on the neck and axilla. Prior ultrasound images showed a prepubertal uterus but normal ovaries. She was not on any medication other than eflornithine hydrochloride for her hirsutism. Genetic testing from outside hospital was also negative, with a 46 XX karyotype and a negative screen for congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency.

Lab work-up for presumed virilization revealed that her total serum cortisol level was mildly elevated, measuring 22.4 mcg/dL (normal range: 2-17 mcg/dL). She also had elevated levels of 17-OH progesterone (326 ng/dL; normal range:16-283 ng/dL) and 17-alpha hydroxyprogesterone (314 nmol/L; normal range:16-283 ng/dL), as well as serum androstenedione (805 ng/dL; normal range for adult female: 22-225 ng/dL) and testosterone (301 ng/dL; normal for adult female: <41 ng/dL). Her dehydroepiandrosterone (453 μg/dL; normal range: 137-1489 μg/dL) and estradiol (66 pg/mL; normal for adult female: 34-170 pg/mL) were within normal limits. Her fasting insulin was elevated (32 uIU/m) with a fasting glucose of 93 mg/dL, suggesting significant insulin resistance that was further corroborated with an elevated calculated homeostasis model assessment of insulin resistance of 7.3 [1]. The remainder of her lab values were unremarkable.

On surveillance imaging, it was noted that there had been interval enlargement and alteration of the enhancement pattern of one of the adenomas in segment 4A. This development prompted an ultrasound guided liver mass biopsy, which showed beta catenin subtype of hepatic adenoma, but also abnormal hepatic proliferation and positive glutamine synthetase, consistent with malignant degeneration to well-differentiated hepatocellular carcinoma. Given the size and bilateral location of her liver masses, and possibility of other lesions undergoing malignant transformation, local resection was felt not to be a curative option. Liver transplantation was recommended but was refused by the patient and her family. The decision was thus made to treat the biopsy proven segment 4A hepatocellular carcinoma with locoregional combination therapy consisting of transarterial chemoembolization and microwave ablation.

Approximately 5 months later on follow-up imaging, a segment 6 liver mass that previously measured 3.8 × 3.5 cm (Fig. 1A) was noted to be growing, measuring 4.5 × 4.1 cm (Fig. 1B). Her growing segment 6 liver mass was presumed to also be undergoing malignant transformation, given her known prior hepatocellular carcinomaHCC. The segment 6 liver mass was thus treated with segmental bland embolization using 100-300 μm microspheres (Embosphere; Merit Medical Systems Inc., South Jordan, UT; Fig. 2A and B). The lesion was subsequently treated with microwave ablation (Neuwave Medical Inc, Madison, WI) using 3 PR-15 probes for 10 minutes at 65 watts (Fig. 2C and D). She tolerated the combination therapy well and her immediate follow-up imaging showed no suspicious residual enhancement, consistent with a complete response (Fig. 2E).

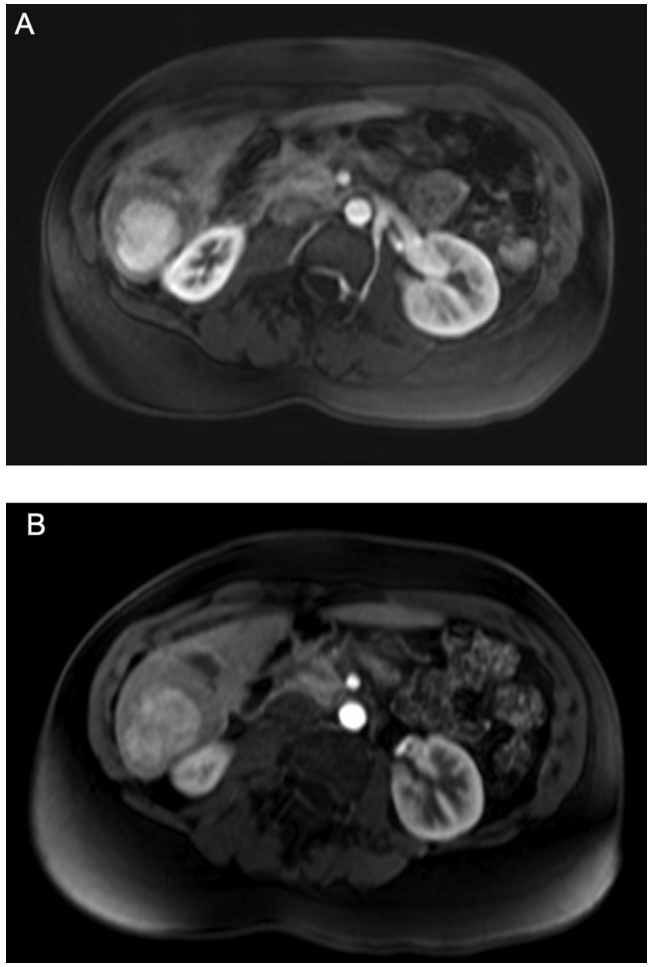

Fig. 1 – Axial T1 fat saturation postcontrast imaging demonstrating the (A) original segment 6 hepatic adenoma of the beta-catenin subtype and (B) interval growth 3 months later. A separate liver lesion had previously been biopsied and found to be positive for malignant transformation to well-differentiated hepatocellular carcinoma

On follow-up imaging after therapy, it was noted that her extrahepatic portal vein drained directly into the inferior vena cava (Fig. 3). There was a short main portal vein extending from the confluence of the superior mesenteric and splenic vein, with a broad communication to the inferior vena cava, and no visible intrahepatic portal vein. This venous anomaly was consistent with a Type 1b Abernethy malformation.

Medical treatment with a maximal dose of metformin 2 g/day was initiated as a non-invasive approach to improve her insulin sensitivity with the intent to decrease her circulating

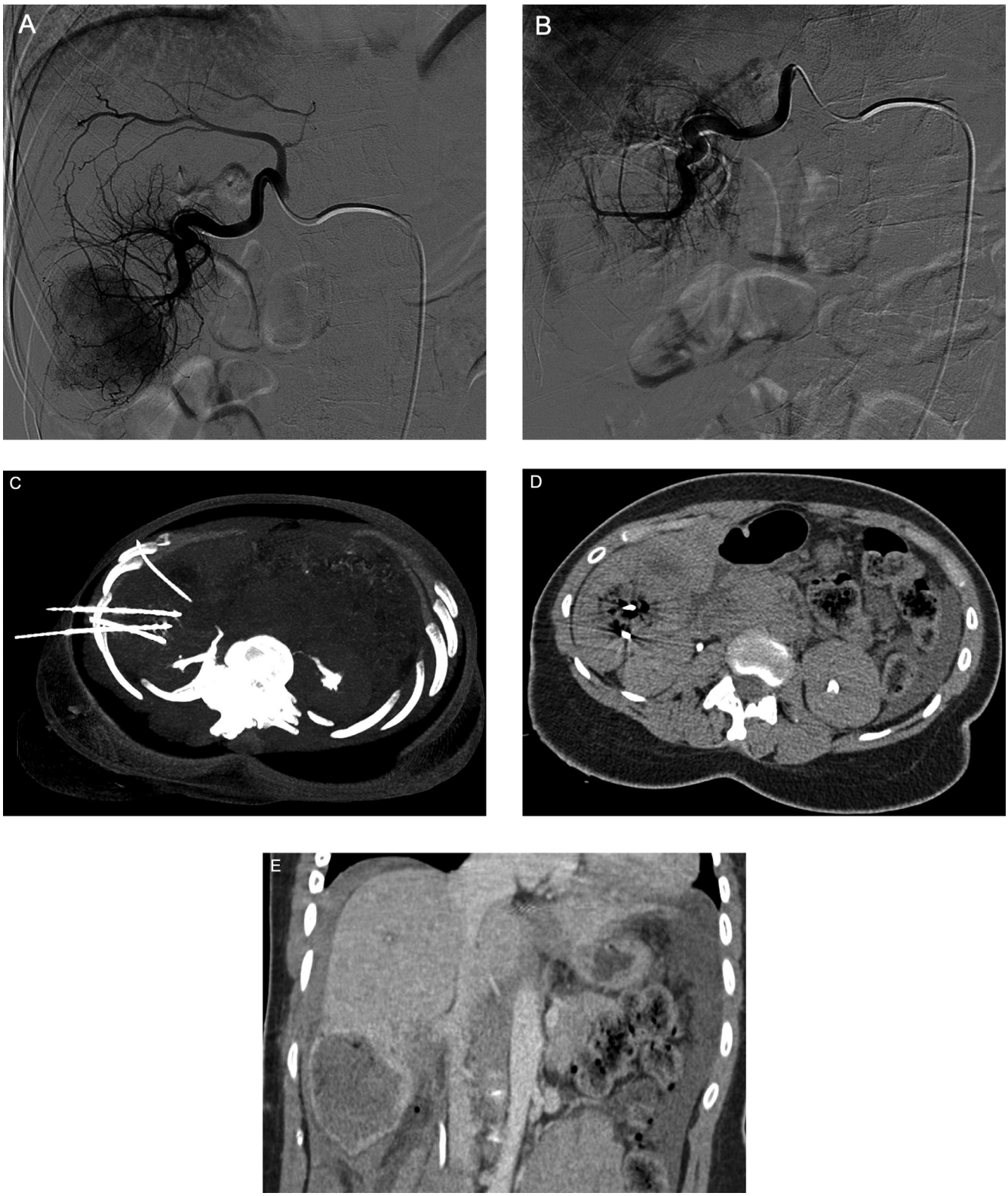

Fig. 2 – (A) Hepatic angiogram demonstrating large enhancing lesion in segment 6, supplied by the right hepatic artery. The segment 6 lesion was embolized with 100-300 μm Embospheres. (B) Postembolization angiogram shows no residual enhancement of the liver mass. Approximately 1-week after embolization the patient underwent CT-guided microwave ablation. (C) Maximum intensity projection of 3 Neuwave PR-15 microwave ablation probes positioned within the segment 6 lesion. The anteriorly-placed catheter was used to administer saline for hydroinfusion. (D) Postablation axial and (E) coronal CT shows complete ablation of the mass with no residual enhancement

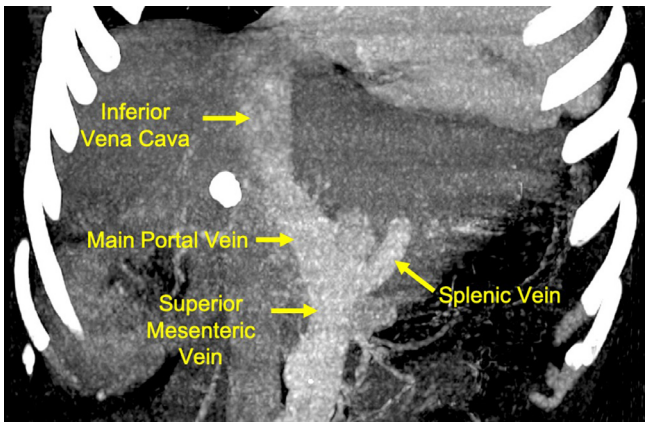

Fig. 3 – Congenital portosystemic shunts are characterized by the absence of the intrahepatic portal vein. Coronal contrast-enhanced CT maximum intensity projection shows the splenic vein and superior mesenteric vein coming together to form a short segment of the main portal vein, which then forms a broad confluence with the inferior vena cava. No intrahepatic portal vein is identified. Note the hyperdense region in segment 4A where a biopsy-confirmed hepatocellular carcinoma was noted and underwent combination transarterial chemoembolization and microwave ablation therapy

insulin levels, and improve the ovarian androgen production. However, on her 8-week follow-up, medical therapy did not improve her hyperandrogenemia. Her testosterone levels remained at level consistent with an adult male range of 288 ng/dL (normal female range 2-45 ng/dL), with no improvement in the androstenedione at 6.79 ng/mL (normal female range 0.260-2.140 ng/mL) and no improvement in the 17-OH progesterone at 261.59 ng/dL (normal female range ≤206.00 ng/dL). Closure of the portosystemic shunt was considered, but the short, broad nature of the portosystemic shunt did not allow for transvenous embolization, and the risk of surgical ligation was deemed to exceed the potential benefit given the lack of encephalopathy and her overall mild symptoms.

Discussion

Congenital portosystemic shunts (CPSS), also known as Abernethy malformations, were first described by John Abernethy in 1793 as a rare congenital absence of the portal vein leading to a primarily extrahepatic portosystemic shunt [2]. In the classification system proposed by Morgan et al, a type 1 CPSS is characterized by the portal vein flow being completely diverted to the systemic circulation with absence of any intrahepatic portal vein component [3]. Type 1 CPSS can be further divided into two subcategories: 1a – separate drainage of the superior mesenteric vein and splenic vein into systemic vein such as the inferior vena cava, right atrium or iliac veins, and 1b – the superior mesenteric vein and splenic veins form a short extra-hepatic portal vein that drains into a systemic venous circulation. In type 2 CPSS, there is a partially formed intrahepatic portal vein system, in conjunction with a shunt between the extrahepatic portal system and systemic circulation [4]. Persistent shunts from CPSS leads to chronic reduction in enterohepatic circulation, resulting in liver atrophy and diminished liver reserve and subsequent hepatic encephalopathy, hepatopulmonary syndrome, and pulmonary hypertension [5–8]. Closure of these shunts has been shown to be effective in resolving or reducing the hyperammonemia or liver failure leading to hepatic encephalopathy [6,7,9]. Untreated portosystemic shunts from CPSS have also been associated with the development of hepatic neoplasms such as FNHs and adenomas, which have been reported to resolve after shunt closure [10]. Metabolic dysfunction such as hyperammonemia or galactosemia is commonly reported, although other less common biochemical alterations have been seen that can lead to hyperandrogenism, primary amenorrhea or signs of virilization [11–13]. For these rare but commonly asymptomatic presentations, CPSS may not be detected for decades and are often discovered as an incidental finding during cross sectional imaging.

There is a strong association of development of liver masses such as focal nodular hyperplasia or hepatocellular adenomas in patients with known CPSS. This association has been hypothesized to be related to the lack of portal vein flow leading to compensatory arterial hyperperfusion and formation of regenerative nodules. Although rare, these neoplasms may degenerate to hepatocellular carcinoma [14–16]. Imaging characteristics of these hepatic neoplasms can be challenging due to the absence of intrahepatic portal systems and their associated portal venous or delayed imaging patterns. For these reasons, biopsy of these lesions is critical if there has been interval growth or a change in enhancement pattern. The literature surrounding the treatment of liver lesions associated with Abernethy malformations is presently limited to case reports and small case series, and usually based on transplant-guidelines such as EASL [14,16,17].

While uncommon, hyperandrogenism in patients with CPSS has been previously reported, although its etiology is unclear [11]. A proposed mechanism centers on the pancreatic excretion of insulin, which is normally removed by the liver via intrahepatic portal vein circulation [11]. CPSS anatomy forces the secreted insulin to bypass the liver, which introduces high levels of insulin into the systemic circulation. Hyperinsulinemia can stimulate androgen production in both the ovaries and adrenal gland via upregulation of 17-alpha-hydroxylase, leading to virilization that is commonly seen in other insulin-resistant states such as polycystic ovary syndrome, diabetes mellitus or lipodystrophic syndrome [18,19]. A marked androstenedione elevation, as seen in this case, may be indicative of an ovarian etiology of the hyperandrogenism given that androstenedione is a predominantly ovarian androgen under hyperstimulation [20]. Modulating systemic insulin levels by increasing insulin sensitivity or reducing insulin secretion can potentially reverse symptoms of virilization or primary amenorrhea, although a pharmacologic approach to this end with metformin was not found to have a significant benefit in this case [18]. Given the lack of efficacy, other insulin sensitizing agents such as thiazolidinediones were not considered given higher risk of toxicities of these alternative agents.

Diagnosis of CPSS is important when treating liver lesions because of the lack of portal vein supply to the liver lobes. If

performing trans-arterial therapy, there is a potential risk of embolizing the only viable blood supply to the targeted liver lobe and increasing the risk for infarction. Fortunately, the patient discussed in this case report tolerated the embolization component well, likely due to the superselective technique used in embolization. In cases of liver malignancy in the setting of known CPSS anatomy, trans-arterial radioembolization has been performed due to their minimal embolic effect and less severe postembolization syndrome [15]. However, there is also growing evidence that the intrahepatic portal vein system, while hypoplastic in cases of CPSS, may be visualized via balloon occlusion venography, as evidenced by 2 recent retrospective studies [17,21]. These studies demonstrated that occlusion venography and shunt closure via surgical ligation or occlusion devices resulted in re-perfusion of the diminutive and dysplastic branches of the intrahepatic portal vein. As advances in imaging resolution and flow characterization with computed tomography or magnetic resonance imaging continues to progress, these smaller portal veins may become more readily identified.

Undiagnosed CPSS can represent an etiology for hyperammonemia, liver failure and hepatopulmonary congestion. The patient described in this case report presented with hyperandrogenism and the development of liver lesions, but was otherwise asymptomatic. Recognizing this anatomic variant early can allow for less invasive interventions such as shunt closure via embolization or surgical ligation prior to the onset of liver failure or metabolic derangements. Early recognition can also allow for potential pharmaceutical interventions to manage virilization or primary amenorrhea in female patients. Advances in cross sectional magnetic resonance or computed tomography imaging, as well as angiography will continue to play an increasingly important role in diagnosing patients with CPSS.

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