CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 39-2022: A 31-Year-Old Woman with Postpartum Abdominal Pain and Fever

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PRESENTATION OF CASE

Dr. Megan E. Bunnell (Obstetrics and Gynecology): A 31-year-old woman was admitted to this hospital 15 days after the birth of her first child because of abdominal pain and fever.

The patient had received routine prenatal care at this hospital. Serologic screening during the pregnancy showed immunity to rubella. Rectovaginal culture was positive for group B streptococcus. Tests for syphilis, hepatitis B virus surface antigen, gonorrhea, chlamydia, and human immunodeficiency virus were negative.

Sixteen days before this admission, the patient went into labor at 38 weeks 1 day of gestation. She was admitted to this hospital. The white-cell count was 13,800 per microliter (reference range, 4500 to 11,000), and the hemoglobin level was 14.0 g per deciliter (reference range, 12.0 to 16.0); treatment with intravenous penicillin was started. On hospital day 2, an epidural anesthetic agent was administered. Artificial rupture of the membranes revealed clear, odorless fluid, and infusion of oxytocin was started. Six hours after artificial rupture of the membranes, the patient gave birth to a healthy baby by vaginal delivery. Three minutes later, the placenta was delivered intact. Immediately after delivery, hemorrhage due to uterine atony occurred; there was an estimated blood loss of 500 ml. Bimanual massage of the uterus was performed, and oxytocin and methylergonovine were administered; hemostasis was subsequently achieved. A perineal laceration was repaired. The patient began breast-feeding, and on postpartum day 1, she was discharged.

Six days before the current admission, on postpartum day 9, pain in the left upper quadrant developed. The pain was dull, radiated to the left flank and back, and was worse with movement and deep breathing. The patient presented to a local urgent care clinic; urine was obtained for culture, and empirical treatment with amoxicillin–clavulanate was started.

Five days before this admission, on postpartum day 10, abdominal pain persisted, and a fever with a temporal temperature of 38.3°C developed. The patient sought evaluation in the emergency department of this hospital. She rated the abdominal pain at 10 on a scale of 0 to 10, with 10 indicating the most severe

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pain. A review of systems was notable for nausea and minimal lochia; there was no diarrhea, constipation, dysuria, hematuria, or breast tenderness.

On examination, the abdomen was soft, and there was mild tenderness on palpation of the left upper quadrant, the uterine fundus, the suprapubic region, and the left costovertebral angle. Pelvic examination, including examination with the use of a speculum, revealed no dehiscence, drainage, or hematoma at the site of the perineal laceration repair and no discharge from the cervical os; there was mild cervical motion tenderness. The white-cell count was 20,700 per microliter. The level of hemoglobin was 11.4 g per deciliter. Blood cultures were obtained. The urine culture obtained at the urgent care clinic was positive for group B streptococcus. Other laboratory test results are shown in Table 1. Treatment with ceftriaxone was started, and the patient was admitted to the hospital for presumed pyelonephritis. On hospital day 3, when the fever and abdominal pain resolved, the patient was discharged home to complete a course of amoxicillin.

During the subsequent 2 days, the patient continued to take amoxicillin at home, but fever and abdominal and flank pain returned. On postpartum day 15, when the pain did not abate after she took acetaminophen, she returned to the emergency department of this hospital.

The patient's medical history included high-grade cervical dysplasia that had led to a loop electrosurgical excision procedure 5 years earlier, as well as a ruptured ovarian cyst 3 years earlier and nephrolithiasis on the left side 5 months earlier. The patient had not been pregnant before the recent pregnancy; before this pregnancy, she had taken oral contraceptives for 12 years. She took prenatal vitamins, as well as polyethylene glycol, docusate, acetaminophen, and ibuprofen as needed. She had no known drug allergies. She lived with her husband and newborn infant in an urban area of New England and worked as an office manager. She did not smoke tobacco, drink alcohol, or use illicit drugs. Her mother had multiple sclerosis and her father had coronary artery disease; her brother was healthy.

On examination, the abdomen was soft, and there was mild tenderness in the left upper quadrant and at the left costovertebral angle. There was no tenderness on palpation of the uterine fundus or the suprapubic region and no cervical motion tenderness. The white-cell count was 10,330 per microliter. The hemoglobin level was 11.2 g per deciliter, the alanine aminotransferase (ALT) level 153 U per liter (reference range, 7 to 33), the aspartate aminotransferase (AST) level 44 U per liter (reference range, 9 to 32), and the alkaline phosphatase level 194 U per liter (reference range, 30 to 100). Other laboratory test results are shown in Table 1. The patient was admitted to this hospital. The next day, the hemoglobin level decreased to 9.7 g per deciliter.

Additional studies were performed, and a diagnosis was made.

DIFFERENTIAL DIAGNOSIS

Dr. Sarah E. Little: On postpartum day 10, this 31-year-old woman presented to the hospital with a temperature of 38.3°C and severe pain in the left upper quadrant. The differential diagnosis for postpartum pain and fever is broad. Common causes can generally be grouped into three main categories: postsurgical complications, thrombotic events, and infection.

POSTSURGICAL COMPLICATIONS

It is unlikely that this patient had a postsurgical complication after vaginal delivery. Most such complications (e.g., uterine dehiscence, retroperitoneal bleeding, or an occult injury to nearby organs) result from cesarean delivery. Although she had had a perineal laceration, the repair was found to be intact.

THROMBOTIC EVENTS

A thrombotic complication is also unlikely in this patient. Although the likelihood of thrombotic events is approximately 20 times as high during the first 2 weeks after delivery as it is 1 year later,[1] this patient's history and examination findings do not suggest deep-vein thrombosis or pulmonary embolism. Septic pelvic thrombophlebitis and ovarian-vein thrombosis are possible diagnoses but are more common after cesarean delivery than after vaginal delivery and typically manifest with diffuse abdominal pain or right lower quadrant pain. Postpartum ovarian-vein thrombosis is more common on the right side than on the left side owing to compression by the physiologic dextrorotation of the uterus and the longer length of the right ovarian vein, which drains directly into the inferior vena cava.[2]

Table 1. Laboratory Data.*

Variable	Reference Range, Adults, This Hospital†	Previous Admission, Postpartum Day 10	This Admission, Postpartum Day 15
Blood			
Sodium (mmol/liter)	135–145	138	142
Potassium (mmol/liter)	3.4–5.0	3.5	3.9
Chloride (mmol/liter)	98–108	103	105
Carbon dioxide (mmol/liter)	23–32	21	26
Urea nitrogen (mg/dl)	8–25	8	8
Creatinine (mg/dl)	0.60–1.50	0.56	0.56
Glucose (mg/dl)	74–106	132	98
Lactic acid (mmol/liter)	0.5–2.0	1.6	0.9
Alanine aminotransferase (U/liter)	7–33	—	153
Aspartate aminotransferase (U/liter)	9–32	—	44
Alkaline phosphatase (U/liter)	30–100	—	194
Total bilirubin (mg/dl)	0.0–1.0	—	0.3
White-cell count (per μl)	4500–11,000	20,700	10,330
Differential count (per μl)			
Neutrophils	1800–7700	17,190	7470
Lymphocytes	1000–4800	1850	1630
Monocytes	200–1200	1360	770
Eosinophils	0–900	30	250
Basophils	0–300	10	80
Hemoglobin (g/dl)	12.0–16.0	11.4	11.2
Hematocrit (%)	36.0–46.0	34.9	34.0
Platelet count (per μl)	150,000–400,000	218,000	392,000
Urine			
Bilirubin	Negative	Negative	Negative
Urobilinogen	Negative	1+	Negative
Blood	Negative	2+	2+
Glucose	Negative	Negative	Negative
Ketones	Negative	Trace	Negative
Leukocyte esterase	Negative	2+	1+
Nitrites	Negative	Negative	Negative
Red cells (per high-power field)	0–2	10–20	10–20
White cells (per high-power field)	<10	20–50	<10

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

INFECTION

Could this patient's presentation be due to an obstetrics-related infection, such as endometritis; infection associated with retained products of conception, mastitis, or an epidural abscess; or infection at the surgical site? Among these pos-

sible infection-related diagnoses, only endometritis is consistent with this patient's history and examination findings; the classic triad of manifestations is fever, leukocytosis, and abdominal pain or tenderness. In patients with endometritis, the pain or tenderness is typically located near the uterine fundus and is associated with foul-smelling discharge. This patient has no common risk factors for this condition, such as cesarean delivery (which is associated with a risk of endometritis that is 10 to 30 times as high as that associated with vaginal delivery)[3] or prolonged labor.[4]

Several nonobstetrics-related infections, including appendicitis, pyelonephritis, and cholecystitis, are also common during the postpartum period. This patient's abdominal pain on the left side that is associated with tenderness at the costovertebral angle, in combination with a positive urine culture, is consistent with a diagnosis of pyelonephritis. Pyelonephritis is common during pregnancy owing to hormone-mediated smooth-muscle relaxation and extrinsic uterine compression, which increase urinary stasis. This patient also has a history of nephrolithiasis, which increases her risk of complicated urinary tract infections, and the oral antibiotic this patient took would have treated many causes of cystitis. However, the number of white cells in the urine (20 to 50 per high-power field) is not as high as might be expected in a patient with pyelonephritis, and no nitrites were present in the urine. The positive urine culture for group B streptococcus might have been a reflection of the patient's known colonization with group B streptococcus, a finding that was based on the rectovaginal culture that had been obtained during pregnancy.

UNCOMMON CAUSES OF ABDOMINAL PAIN

On postpartum day 15, the patient continued to have clinically significant pain in the left upper quadrant. At this point, I would be concerned about uncommon causes of left upper quadrant pain, such as splenic infarction, torsion due to a wandering spleen, or rupture of a splenic-artery aneurysm. However, the patient has no risk factors for splenic complications, such as trauma, sickle-cell disease, or a connective tissue disorder, and the results of tests of liver function were abnormal, which I would not expect in a patient with a splenic complication. Although alkaline phosphatase is produced by the placenta and the level is typically elevated during pregnancy, it quickly returns to a normal level after delivery.[5] Furthermore, the level of hemoglobin decreased from 11.2 g per deciliter to 9.7 g per deciliter during the current admission. In the absence of ongoing vaginal bleeding, which the patient presumably does not have, I would be very worried about internal bleeding and would perform abdominal imaging.

ABDOMINAL IMAGING

Dr. Onofrio A. Catalano: A transverse ultrasound image of the left lobe of the liver (Fig. 1A) showed a large exophytic, heterogeneous lesion. Computed tomography (CT) (Fig. 1B and 1C), performed before and after the administration of oral and intravenous contrast material, confirmed the presence of an exophytic mass arising from the left hepatic lobe and exerting mass effect on the stomach. The mass measured 11.1 cm by 9.5 cm by 10.8 cm and contained spontaneously hyperdense material that did not enhance after the administration of contrast material, a finding that was consistent with hematoma. A large nonenhancing component, which was most likely necrotic, and some vividly enhancing peripheral components were also seen within the mass.

There was no biliary dilatation in the left hepatic lobe. No radiologic signs of cirrhosis, lymphadenopathy, or peritoneal or other metastases were identified.

DIFFERENTIAL DIAGNOSIS AFTER ABDOMINAL IMAGING

Dr. Little: Liver complications that are specific to pregnancy include preeclampsia with severe features, HELLP (hemolysis, elevated liver-enzyme levels, and low platelet count) syndrome, and acute fatty liver of pregnancy.

HELLP SYNDROME

HELLP syndrome can be complicated by formation of a subcapsular hematoma, although such an event is rare (<1% of cases).[6] The pathophysiological process of subcapsular hematoma formation is thought to start with microangiopathy and vasospasm that in turn lead to the development of ischemic intrahepatic lesions. Neovascu-

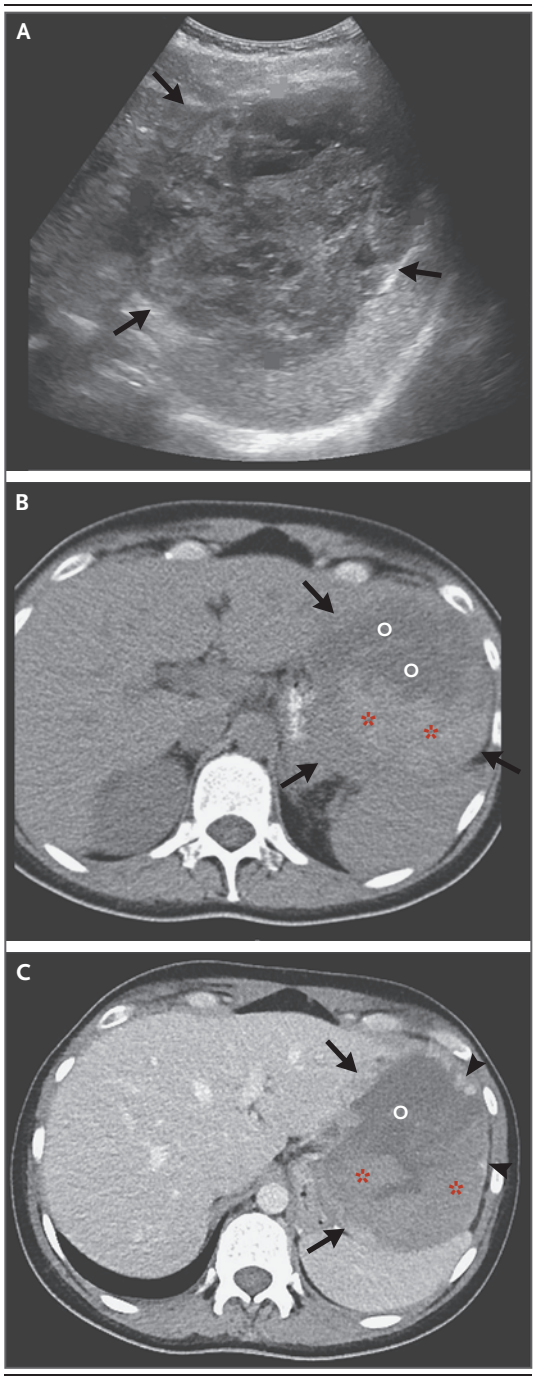

Figure 1. Imaging Studies of the Abdomen.

A transverse ultrasound image of the left lobe of the liver (Panel A) shows a large exophytic, heterogeneous lesion (arrows). CT images obtained before (Panel B) and after (Panel C) the administration of oral and intravenous contrast material confirm a large exophytic mass (arrows) arising from the left hepatic lobe and exerting mass effect on the stomach. The mass contains spontaneously hyperdense material that does not enhance after administration of the contrast material (asterisks) and is consistent with hematoma, a large nonenhancing component that is most likely necrotic (circles), and some vividly enhancing peripheral components (arrowheads).

larization is complicated by hemorrhage in the context of labile hypertension. This intrahepatic blood collects in the subcapsular space, which can cause pain as Glisson's capsule stretches and can even lead to capsular rupture with potentially catastrophic intraabdominal hemorrhage.[6-8] Could this patient have a subcapsular hematoma resulting from HELLP syndrome?

This diagnosis is unlikely, given that she has no other features of severe preeclampsia or HELLP syndrome; she is normotensive and has no other laboratory abnormalities, such as hemolysis (the total bilirubin level is normal) or thrombocytopenia. In addition, this admission is 15 days after delivery; although severe preeclampsia and HELLP syndrome can occur during the postpartum period, their occurrence as a first presentation would be unusual more than 2 weeks after delivery.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy is an uncommon complication — occurring in 1 in 1000 to 1 in 35,000 deliveries[9] — that results from an accumulation of fatty acid metabolites in hepatocytes due to defects in fatty acid metabolism. Acute fatty liver of pregnancy can be associated with fetal long-chain 3-hydroxyacyl–coenzyme A dehydrogenase deficiency. If the fetus is homozygous for the genetic mutation that causes this enzyme deficiency and the mother is therefore an obligate carrier, fatty acid metabolites build up in the fetal liver and ultimately in the maternal liver. The diagnosis of acute fatty liver of pregnancy is unlikely in this patient because it is much more commonly diagnosed in the third trimester or during the immediate postpartum period. In addition, the patient's imaging findings are not consistent with this diagnosis, since I would have expected the presence of diffuse fatty infiltrate. Moreover, her laboratory test results are not consistent with this diagnosis; acute fatty liver of pregnancy is associated with marked liver dysfunction that leads to clinically significant hypoglycemia, elevated bilirubin levels, thrombocytopenia, and elevations in liver-function

test results, which are typically many times as high as the upper limit of the normal range.[10]

HEPATIC INFARCTION

What about other liver diseases that are not specific to pregnancy? I would consider four main categories: benign lesions, cancer, infection, and infarction. Could this patient have hepatic infarction? She had increased postpartum bleeding, and it is possible that ischemic infarction developed. However, she has no other hypovolemic complications, such as Sheehan's syndrome (necrosis of the anterior pituitary gland after a postpartum hemorrhage), and if she had hepatic infarction, I would have expected a wedge-shaped pattern on imaging.

HEPATIC ABSCESS

Could a liver abscess have developed in this patient? This diagnosis seems unlikely; she has no risk factors for liver abscess (she had a vaginal delivery without pelvic infection), and a large lesion such as that seen in this patient would typically occur in conjunction with multiple intra-abdominal abscesses, a high degree of leukocytosis, and sepsis.

NEOPLASMS

This patient has no history of cancer, which makes metastatic liver disease unlikely, and she has no risk factors (such as cirrhosis or chronic hepatitis) for hepatocellular carcinoma. It is possible that she has a rare primary cancer, such as lymphoma or cholangiocarcinoma, but I would expect a patient with cancer to present with jaundice or an incidental mass rather than with pain and fever. Moreover, the mass is hemorrhagic, which would also be unusual for cancer.

BENIGN LESIONS

Thus, the most likely diagnosis in this patient is a benign liver lesion, such as hemangioma, focal nodular hyperplasia, or adenoma. Although hemangiomas and focal nodular hyperplasia of the liver can grow as a result of estrogen exposure during pregnancy, the patient's imaging findings are not characteristic of these lesions, and such lesions do not tend to bleed.

Hepatic adenomas, although uncommon overall, are more common among women than among men and are up to 30 or 40 times as common among long-term users of oral contraceptives as among those who do not use oral contraceptives.[11] This patient was using oral contraception for 12 years. Hepatic adenomas are also known to grow as a result of estrogen exposure during pregnancy and are complicated by bleeding in up to 30% of all cases. Risk factors for bleeding include pregnancy and a large lesion; lesions larger than 5 cm are considered to confer a higher risk, and this patient's lesion was more than twice that size. Also, adenomas on the left side of the liver (segments 2 and 3) are more than twice as likely to bleed as those on the right side,[12] which is consistent with the patient's abdominal pain on the left side. Leukocytosis and fever could be explained by general inflammation from the hemorrhage but also could be consistent with an inflammatory subtype of hepatic adenoma.

There are three main subtypes of hepatic adenomas: the subtype associated with mutation of *HNF1A* (the gene that encodes hepatocyte nuclear factor 1A), the subtype associated with beta-catenin activation, and the inflammatory subtype. The inflammatory subtype is associated with elevated levels of inflammatory markers in the blood and is also the subtype that is most likely to cause bleeding.[13] Hepatic adenomas are typically painless lesions, but in the context of acute bleeding and stretching of the liver capsule, I would expect pain to be present. Given the large lesion and the associated hemorrhage, I would recommend surgical resection of the lesion.

CLINICAL IMPRESSION AND MANAGEMENT

Dr. Andrea G. Edlow: Aspects of the patient's initial presentation were confusing. The group B streptococcus bacteriuria, the temperature of 38.3°C, the white-cell count of 20,700 per microliter, the flank pain on the left side, and the apparent tenderness at the costovertebral angle were suggestive of pyelonephritis. Although the initial urinalysis did not reveal as many white cells as would be typical for pyelonephritis, the patient had started a course of empirical treatment with amoxicillin–clavulanate after her urgent care visit (6 days before the current admission), so it was possible that the infection was partially treated. Although the mild tenderness on palpation of the uterine fundus could have been in-

dicative of endometritis, the vaginal delivery, the absence of prolonged artificial rupture of the membranes, the spontaneous delivery of an intact placenta, and the absence of cervical motion tenderness on examination all made the diagnosis of endometritis unlikely. During the initial admission for suspected pyelonephritis on postpartum day 10, the patient was treated with intravenous ceftriaxone, and the pain and fever resolved initially. She was discharged home on hospital day 3 to complete the remainder of an oral course of amoxicillin but returned to the hospital after she had recurrence of abdominal pain and fever, despite the continued use of amoxicillin.

After the patient presented for the third time with these symptoms, on postpartum day 15, CT of the abdomen and pelvis was performed; a heterogeneous mass with mixed attenuation was identified in the left lobe of the liver. The white-cell count was 10,330 per microliter on readmission — a decrease from a level of 20,700 per microliter obtained 5 days earlier. This decrease in white-cell count may have been the result of partial treatment of a superimposed urinary tract infection. The hemoglobin level was 11.2 g per deciliter on admission on postpartum day 15 but decreased to 9.7 g per deciliter on repeat testing, a finding that was thought to indicate hemorrhage into the liver mass, given the increased abdominal pain and no other identified source of bleeding. The blood levels of tumor markers (including alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9) were found to be normal, thereby reducing, but not eliminating, the possibility of cancer. The results of liver-function tests were elevated, with an AST level of 44 U per liter and an ALT level of 153 U per liter. Review of the patient's liver-function test results obtained 3 years earlier, outside of pregnancy, also revealed elevated AST and ALT levels (44 U per liter and 40 U per liter, respectively), which suggests the possibility of a long-standing process with a relatively recent change in pregnancy.

After consideration of the findings on abdominal imaging and the normal levels of tumor markers, the suspected diagnosis was hepatic adenoma. The general surgery service was consulted. Given the size of the mass and the decrease in hemoglobin level — findings that suggested intralesional hemorrhage — surgical resection was recommended. On hospital day 2, the patient underwent exploratory laparotomy, left lateral segmentectomy, and resection of a hepatic mass (measuring 16 cm by 13 cm) involving the left lateral segment of the liver and the left hemidiaphragm. Blood transfusion was deemed to be unnecessary. She recovered well and was discharged home on hospital day 5.

CLINICAL DIAGNOSIS

Hepatic adenoma.

DR. SARAH E. LITTLE'S DIAGNOSIS

Hepatic adenoma, most likely an inflammatory subtype.

PATHOLOGICAL DISCUSSION

Dr. Stuti G. Shroff: We received a resection specimen comprising a portion of the liver (weighing 760 g and measuring 15.9 cm in length) and the attached hemidiaphragm (Fig. 2). The hepatic capsular surface was smooth and dull. Sectioning of the specimen revealed a 15.9-cm mass that was predominantly hemorrhagic with a tan-to-yellow, soft, centrally necrotic cut surface; the mass was located 0.2 cm from the transected margin of the liver and 0.3 cm from the diaphragmatic margin. Fifty percent of the mass was hemorrhagic and approximately 30% was necrotic, with possible viable tumor along the periphery of the specimen.

Histologic examination revealed a benign, microscopically encapsulated hepatic tumor with unpaired thick-walled vessels (Fig. 3A and 3B). The hepatic trabeculae in the tumor were uniformly 1 to 2 cells thick with no cytologic atypia and no discernible mitoses. Immunohistochemical staining was performed to further characterize the tumor. The tumor cells showed retained expression of liver fatty acid–binding protein (not shown), membranous expression of beta-catenin (not shown), focal minimal perivascular and parenchymal staining with glutamine synthetase at the periphery of the tumor (Fig. 3C), and patchy staining with serum amyloid A (Fig. 3D). The overall morphologic features and immunohistochemical findings supported the diagnosis of inflammatory-type hepatic adenoma with associated ischemic necrosis and

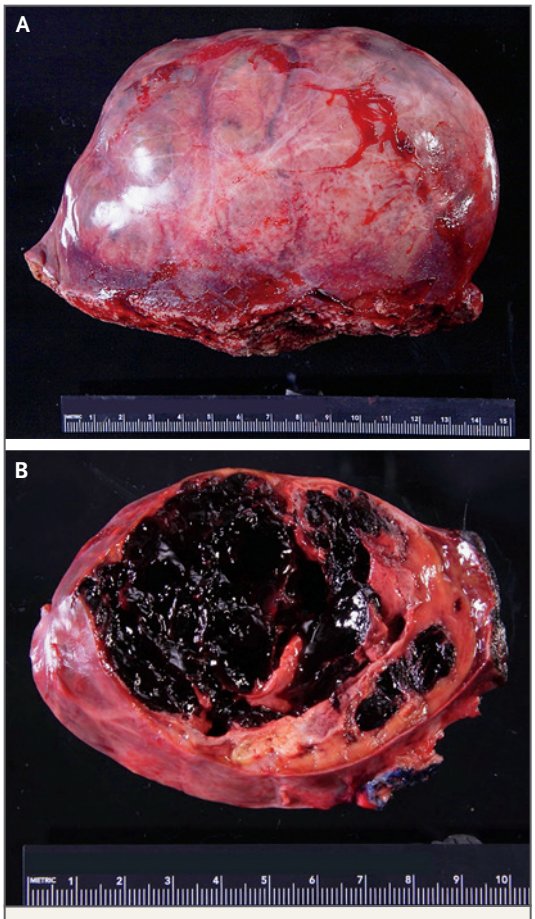

Figure 2. Hepatic-Resection Specimen for Gross Examination.

On gross examination, the solitary resected mass measures 15.9 cm in length, is hemorrhagic, and is found to be confined to the liver (Panel A). The cut surface is tan-to-yellow, soft, and centrally necrotic (Panel B).

extensive hemorrhage. The tumor was confined to the liver, with adhesions between the hepatic capsule and diaphragm.

PATHOLOGICAL DIAGNOSIS

Hepatic adenoma, inflammatory type, with associated ischemic necrosis and extensive hemorrhage.

FOLLOW-UP

Dr. Edlow: The patient was seen in the clinic at 8 weeks postpartum. She reported no abdominal pain or other symptoms. Because estrogen-containing contraception was contraindicated

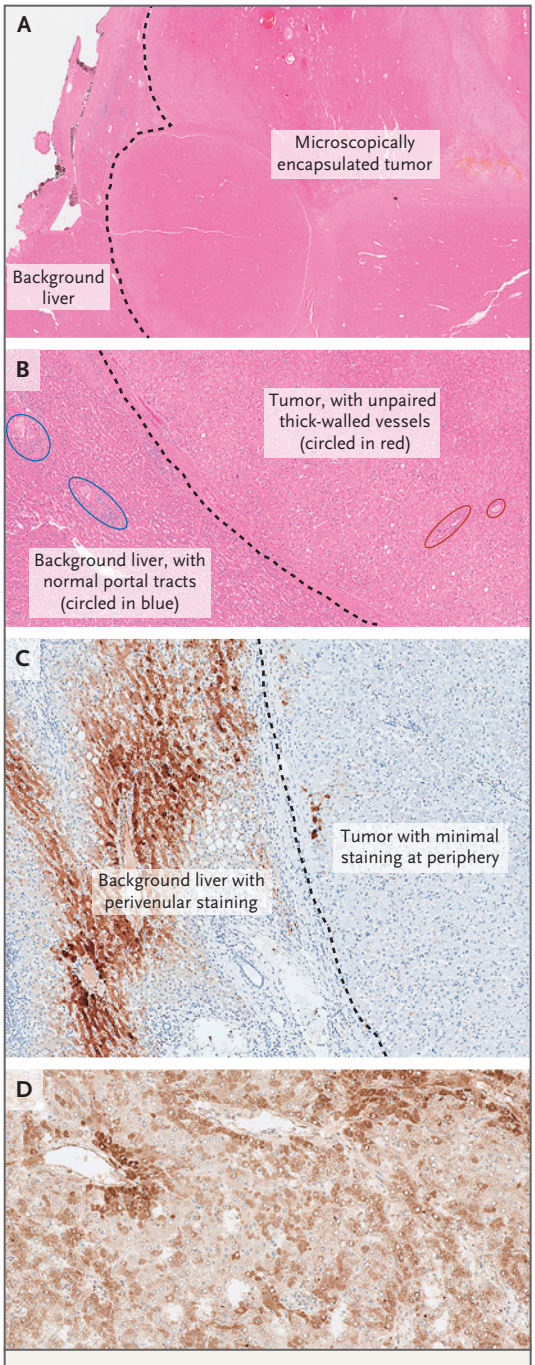

Figure 3. Hepatic-Resection Specimen for Microscopic Examination.

On microscopic examination, hematoxylin and eosin staining shows a benign, microscopically encapsulated hepatic tumor (Panel A). Numerous unpaired thick-walled vessels are identified in the tumor (Panel B). The hepatic trabeculae are noted to be 1 to 2 cells thick. Immunostains show very focal tumor-cell positivity for glutamine synthetase (Panel C) and patchy staining with serum amyloid A (Panel D).

given the diagnosis of hepatic adenoma,[14] an etonogestrel (progesterone-only) implant was placed for postpartum contraception. The patient continued to have mildly elevated liver-function test results; the ALT level was 48 U per liter and the AST level 33 U per liter. The general surgery service recommended performing repeat magnetic resonance imaging or CT if the patient becomes symptomatic, and the obstetrics service recommended resection of any larger adenoma (i.e., a lesion >5 cm) before any subsequent pregnancy.

FINAL DIAGNOSIS

Hepatic adenoma.

This case was presented at Obstetrics and Gynecology Grand Rounds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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