



Case report

Paraneoplastic nodular regenerative hyperplasia of the liver associated with placental site trophoblastic tumor

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1. Introduction

Gestational trophoblastic neoplasia (GTN) encompasses a spectrum of diseases, including invasive hydatidiform mole, choriocarcinoma, epithelioid trophoblastic tumor (ETT), and placental site trophoblastic tumor (PSTT). All arise from the placental trophoblast, which normally differentiates into cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. PSTT and ETT are thought to originate from intermediate trophoblastic cells at the placental implantation site (Lurain, 2010). PSTT is rare; as of 2017 there have been fewer than 500 cases reported in the literature worldwide (Horowitz et al., 2017). Due to its relative chemoresistance, PSTT accounts for a disproportionate incidence of mortality from GTN. The disease course and treatment paradigms for PSTT are only recently being defined.

While paraneoplastic syndromes, including disorders of the nervous system, connective tissue, and skin, as well as hematologic abnormalities and nephrotic syndrome, have been associated with a variety of gynecologic cancers, GTN has not been reported among these. To our knowledge, this is the first report of PSTT presenting with paraneoplastic nodular regenerative hyperplasia (NRH) of the liver.

NRH-L is an uncommon liver condition that ranges in severity from occult to overt disease. It is a rare parenchymatous liver disease characterized by diffuse transformation of the hepatic parenchyma into multiple small nodules (Hartleb et al., 2011). In its most severe form, it can present with hepatosplenomegaly and ascites manifesting as non-cirrhotic portal hypertension. NRH-L is often associated with underlying auto-immune diseases, antineoplastic agents, and hematologic malignancies, including myeloproliferative disorders, myeloma, leukemia, and lymphoma (Hartleb et al., 2011) (Barge et al., 2016) (Al-Hamoudia et al., 2009). There are a few reported cases of NRH-L in patients with colorectal cancer in the setting of antineoplastic treatment, as well as a single case report of NRH-L associated with carcinoid tumor (Al-Hamoudia et al., 2009). There is, otherwise, scant literature on NRH-L in the setting of malignant solid tumors, and there are no

documented cases of NRH-L associated with gynecologic malignancies.

2. Case

We present the case of a previously healthy G1P1001 37-year-old Caucasian female with no personal or family history of liver or gynecologic disease. Following an uncomplicated pregnancy, she delivered a healthy female infant via full-term spontaneous vaginal delivery in June 2017. The placenta was delivered with the help of manual extraction 45 min after delivery. Her postpartum course was uncomplicated. She was amenorrheic for 9 months following delivery, as she was taking oral contraception and breastfeeding. She then experienced an isolated episode of abnormal uterine bleeding and, shortly thereafter, a rapid increase in abdominal girth.

In June 2018, she presented to her benign gynecologist with weight gain. Approximately three weeks later, she re-presented to her gynecologist with marked abdominal distension and pitting lower extremity edema. Labs were notable for mildly elevated AST and ALT, hypoalbuminemia, low platelets, elevated CRP, and a positive quantitative hCG of 857 mIU/mL. The patient endorsed abstinence since her delivery 1 year prior. Imaging was ordered and an abdominal ultrasound showed trace ascites and mild splenomegaly. CT demonstrated mild splenomegaly, a recanalized umbilical vein and large volume ascites suggestive of portal hypertension (Fig. 1a). There were no overt cirrhotic features or suspicious focal hepatic lesions. An enlarged heterogeneous uterus with prominent sub-endometrial and parametrial vessels was noted. No adnexal neoplasm or pelvic lymphadenopathy was seen.

She underwent a large volume paracentesis. Cytology was negative for malignancy and ascitic fluid showed a SAAG ≥ 1.1 , consistent with portal hypertension. A transjugular liver biopsy showed histopathologic changes suggestive of nodular regenerative hyperplasia without evidence of fatty change, significant inflammation, or vascular outflow disease. Microscopically, the hepatocytes within the nodule were

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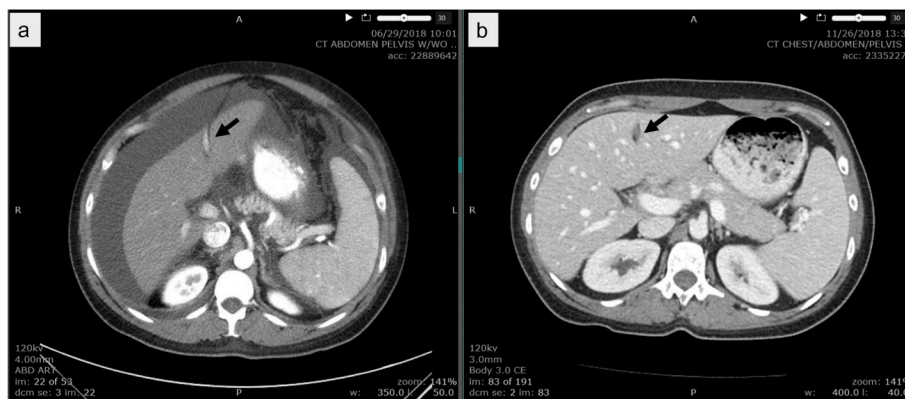


Fig. 1. Presence (a) and resolution (b) of radiographic hallmarks of NRH-L-related non-cirrhotic portal hypertension on CT imaging.

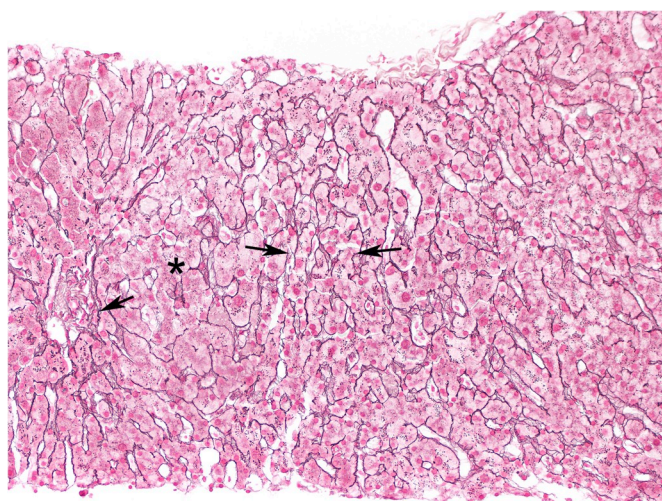


Fig. 2. Liver biopsy with reticulin staining showing NRH-type changes. Star (*), Reticulin stain highlights the nodule. Arrow, the reticulin network is compressed in the parenchyma between the nodules. 200 \times .

enlarged with hypertrophic nuclei and arranged in plates that were several cell layers thick. In contrast, the hepatocytes between individual nodules were atrophic and pressed into thin, parallel plates that were best visualized by a reticulin stain (Fig. 2). Hysteroscopy D&C revealed PSTT. PET CT was negative for metastatic disease but suggested deep myometrial invasion with extension to the serosa.

Subsequently, in August 2018, she underwent a radical abdominal hysterectomy and bilateral salpingectomy with drainage of 5 l of ascites. Her surgery was uncomplicated. There was no concerning lymphadenopathy or evidence of extra-uterine disease other than a large primary uterine mass which appeared to clinically invade into the uterine serosa and cervix. On final pathology, the patient was diagnosed with a stage I PSTT, measuring 11.2 \times 5.4 \times 7.8 cm. Grossly, the tumor mass replaced the endomyometrium and extended to the serosa. Histologically, the tumor displayed an infiltrative growth of aggregated sheets of large, polyhedral to round, predominately mononuclear, placental site intermediate trophoblastic cells (Fig. 3a). Characteristically, the tumor cells completely replaced the vascular wall of myometrial vessels (Fig. 3b). At the periphery, the tumor cells infiltrated and separated myometrial smooth-muscle fibers (Fig. 3c). On higher magnification, the cells contained abundant amphophilic, eosinophilic or clear cytoplasm, and pronounced nuclear atypia with frequent, large, convoluted nuclei and marked hyperchromasia (Fig. 3d).

By postoperative day 13, her peripheral edema and ascites had resolved and she had returned to her baseline weight. Because the patient had a World Health Organization GTN Risk Score of 10 and evidence of

margin involvement, she was deemed to be high risk for recurrence and was offered adjuvant chemotherapy. On postoperative day 37, she started cycle 1 day 1 of adjuvant, multi-agent chemotherapy (EMA-EP). Her pre-chemotherapy β -hCG was undetectable. Following cycle 1, she developed a grade 3 transaminitis and her methotrexate was dose-reduced by 25%. She completed cycle 3 of treatment in November 2018 without further adverse events. Liver function has since improved with near-normalization of her transaminases and resolution of radiographic evidence of portal hypertension (Fig. 1b). Now 6 months out from her original surgery, she continues to have a normal performance status, the ascites and peripheral edema have not returned, and she has discontinued diuretic therapy. Her most recent β -hCG was undetectable, indicating a durable remission.

3. Discussion

PSTT is a rare type of GTN arising from intermediate trophoblastic cells. In the majority of cases, it follows a normal-term, non-molar pregnancy, though it can also follow a molar pregnancy (Zhao et al., 2016) (Lurain, 2010). PSTT is typically slow-growing and uterine-confined disease has an excellent prognosis (100% survival). While PSTT has a propensity for lymphatic metastases, it typically has less vascular invasion than choriocarcinoma (Lurain, 2010). Recommended treatment for stage 1 PSTT consists of hysterectomy and lymph node dissection. In patients with metastatic disease or adverse prognostic factors, chemotherapy (EMA-EP, paclitaxel/cisplatin, or paclitaxel/etoposide) is recommended. The survival rate for metastatic disease is approximately 50–60% (Lurain, 2011).

Due to its rarity, PSTT is poorly understood, and we are less familiar with the disease course of this neoplasm than other gynecologic cancers, including rare tumors. Interestingly, several recent case reports have suggested that paraneoplastic syndromes may herald or accompany a diagnosis of PSTT. Both lupus nephritis and nephrotic syndrome have occurred with PSTT and resolved with definitive surgical management with hysterectomy (Changji et al., 2014) (Sawamura et al., 2018). PSTT-associated erythrocytosis has also been reported to arise and resolve following hysterectomy (Brewer et al., 1992).

In the present case, NRH-L heralded the diagnosis of PSTT and clinically resolved following hysterectomy, suggesting that NRH-L may be a paraneoplastic disorder associated with this subtype of GTN. Despite extensive hepatic management and treatment, the patient only experienced clinical resolution of her NRH-L after she underwent surgical treatment of her PSTT. Furthermore, she continues to demonstrate no evidence of recurrence with adjuvant chemotherapy. Thus, given the synchronous timing of both the onset and resolution of NRH-L and PSTT, we theorize that NRH-L was etiologically paraneoplastic in this case.

Interestingly, NRH-L is not typically described as a paraneoplastic syndrome in the literature. This is likely because it is commonly

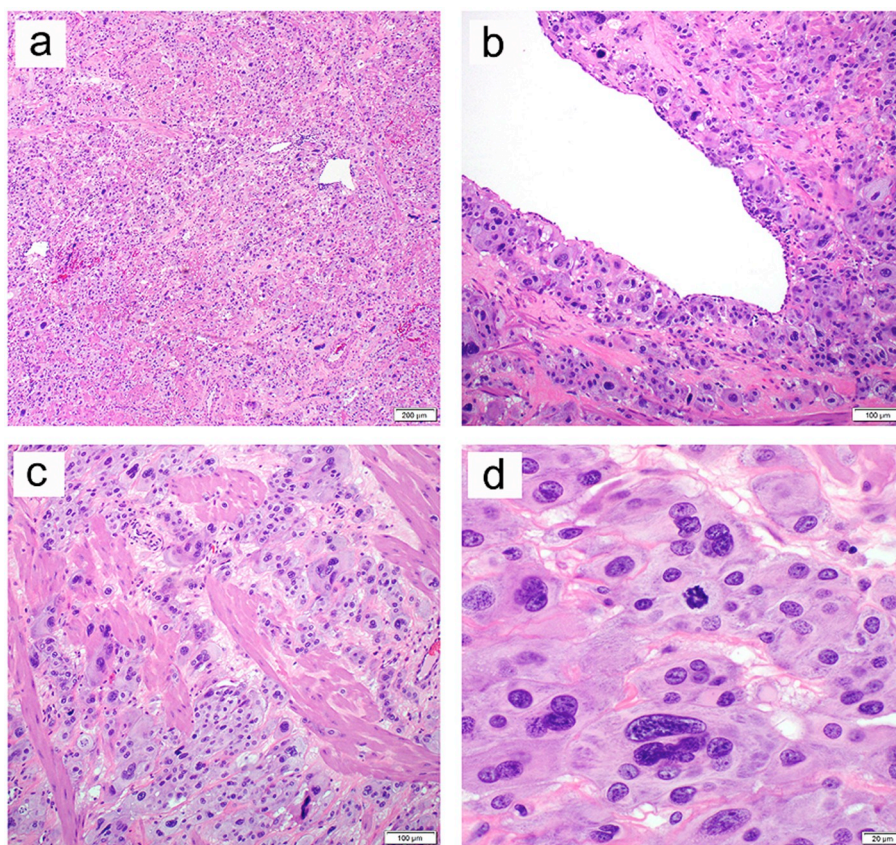


Fig. 3. Representative histologic images of placental site trophoblastic tumor (PSTT). (a) H&E, 40 \times . (b) Perivascular distribution of the tumor cells. 100 \times . (c) the tumor cells infiltrate into the smooth muscle fibers. 100 \times . (d) H&E, 400 \times .

associated with non-malignant diseases, and it has not historically been associated with malignant solid tumors. To date, there are no reported associations with GTN or other gynecologic malignancies. It is possible that NRH-L goes unrecognized, however, and is not reported in association with other diseases. In a case series of 2500 consecutive autopsies, occult NRH-L was uncovered in 2.6% of cases (Wanless, 1990).

Though it is not yet fully understood, NRH-L is thought to arise from abnormalities in portal blood flow, secondary to vasculopathy or acinar damage. Correspondingly, NRH-L is often associated with systemic diseases that give rise to hematologic and vascular dysfunction. It is hypothesized that the local ischemia and atrophy that results from mechanical or functional sinusoidal dysfunction leads to a compensatory hyperplasia of neighboring acini over time, resulting in micronodularity (Ebert, 2016) (Al-Hamoudia et al., 2009). A large study examining the pathogenic role of ischemia found that atrophy and nodular hyperplasia resulted from chronic ischemia, whereas apoptosis most often resulted from acute ischemia (Al-Hamoudia et al., 2009).

Generally speaking, NRH-L does not affect synthetic liver function, so liver transplant is not typically necessary (Ebert, 2016). Once diagnosed, the prognosis of NRH-L is thought to most closely correlate with the severity of the underlying systemic disease, rather than with the severity of the liver disease itself (Barge et al., 2016). Thus, treatment of NRH-L is directed at management of the underlying systemic disease. In this case, treatment of the patient's PSTT with radical hysterectomy and adjuvant chemotherapy resulted in clinical resolution of her NRH-L and sequelae.

Conflict of interest statement

The authors of this paper have no conflicts of interest to disclose.

Author contribution

Kathryn Dumas: data collection, manuscript preparation, and editing the final draft.

MaryAnn Wilbur: surgery, manuscript preparation, and editing the final draft.

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William Cliby: manuscript preparation and editing the final draft.

Carrie Langstraat: manuscript preparation and editing the final draft.

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Deyin Xing: pathology, manuscript preparation, and editing the final draft.

Rebecca L. Stone: manuscript preparation, figure design, and editing the final draft.

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