CASE REPORT

Graves' disease presenting as severe postpartum pruritus

Rachel Marinch Carpenter,^{1,2} Jessica Wongward²¹Family Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA²Family Medicine, Saint Joseph Hospital Family Medicine Residency, Denver, Colorado, USA

Correspondence to

Dr Rachel Marinch Carpenter, rachel.marinch@gmail.com

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SUMMARY

A 39-year-old multigravida woman presented 3 weeks postpartum with worsening generalised pruritus without primary rash. Workup was significant for cholestasis and undiagnosed Graves' disease. She began to have symptomatic relief after starting methimazole, and liver function tests normalised as she became euthyroid.

BACKGROUND

Though hyperthyroidism is a commonly diagnosed disease, we rarely think of pruritus as the sole presenting symptom. In a patient with generalised pruritus in the absence of primary skin lesions, the differential is broad but includes several concerning systemic disorders, including malignancy, renal disease, thyroid disease, liver disease, HIV or parasitic infection. Therefore, in addition to a careful history and examination, laboratory testing is typically warranted. Cholestasis is a reasonable explanation for pruritus. However, this too warrants further investigation to find the underlying aetiology of the cholestasis in order to appropriately treat the disease and its symptoms.

Thyroid disease is uncommonly considered as a cause of liver disease, and the mechanism is not clearly understood. However, there is a plethora of evidence that links thyroid and hepatobiliary disease. If this connection is missed, a patient's symptoms and disease may remain untreated or the patient may be subjected to unnecessary tests, treatments and procedures.

In the following case report, we describe a patient who presented with severe postpartum pruritus due to cholestasis whose symptoms improved following treatment of Graves' disease.

CASE PRESENTATION

A 39-year-old multigravida woman presented to our clinic 3 weeks postpartum with new onset, worsening, severe generalised pruritus. She also reported chronic constipation with haemorrhoids and some mild dry eyes. Her pregnancy was overall uncomplicated. The patient was overall healthy at baseline, with no known dermatological, gastrointestinal, autoimmune, endocrine or psychiatric conditions. She was previously diagnosed with essential hypertension and depression but did not require medications. She was not taking any medications aside from prenatal vitamins and occasional ibuprofen. She did not smoke, drink or use drugs.

She was not breastfeeding and did not wish to become pregnant again.

Initial examination was significant for mild tachycardia (heart rate 110 beats per minute) and obvious discomfort due to continuous scratching. She also had significant generalised skin excoriations with bleeding; no underlying rash was noted, though this was difficult to ascertain given the degree of self-imposed skin destruction from scratching. No jaundice, exophthalmos, thyroid enlargement, organomegaly or abdominal pain were noted on initial examination.

We were initially suspicious of a possible contact or irritant dermatitis versus scabies versus underlying systemic disease. Supportive care with antihistamines was recommended and laboratory workup was initiated.

INVESTIGATIONS

Initial laboratory workup was significant for mildly elevated alkaline phosphatase of 185 U/L (normal 45–117). However, this was difficult to interpret in the setting of her recent pregnancy. Aspartate aminotransferase (AST) was also minimally elevated at 49 U/L (normal 7–37) and gamma-glutamyltransferase (GTT) was elevated at 128 (normal 5–55). Other liver function tests (LFTs) were within normal limits. Likewise, complete blood count and basic metabolic panel were unrevealing.

Due to her mildly abnormal LFTs and intense pruritus, we obtained total bile acids which were significantly elevated at 27 µmol/L (normal 0–10) consistent with a diagnosis of cholestasis.

In an attempt to find the aetiology of the cholestasis, we obtained hepatitis C antibody, which was negative. Hepatitis B surface antigen and HIV were normal during pregnancy. Antimitochondrial antibody, antinuclear antibody, ceruloplasmin and actin antibody were also normal. An iron panel showed mildly decreased percentage of iron saturation at 17% (normal 20%–55%) but no evidence of haemochromatosis. Right upper-quadrant ultrasound revealed normal liver, gall bladder and biliary tract.

Due to failure to improve with ursodiol, thyroid testing was obtained. Thyroid stimulating hormone (TSH) was undetectable at <0.005 µ/mL (normal 0.358–3.740) and free T4 was elevated at 6.66 µ/mL (normal 0.76–1.46). TSH receptor antibody (TRAb) was markedly elevated at 20.85 IU/mL (normal ≤1.75), most consistent with Graves' disease.

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DIFFERENTIAL DIAGNOSIS

Due to the patient's lack of notable primary rash, we were quickly suspicious of a possible underlying systemic disease, such as liver, thyroid or renal disease; HIV and malignancy. However, the possibility of psychogenic itch or contact dermatitis existed, so we attempted to reduce scratching and excoriations to see if a primary rash was present. Antihistamines did not alleviate pruritus. Given her recent pregnancy and abnormal bile acids, an atypical intrahepatic cholestasis of pregnancy (ICP) was considered, but we could not find any case reports of ICP presenting in a similar fashion. Additionally, over a month of ursodiol treatment was ineffective and it was only after her thyroid disease was adequately treated that she improved. However, as bile acids were not checked during pregnancy, ICP cannot be unequivocally excluded. Additional workup for aetiology of cholestasis, such as primary biliary cholangitis or primary sclerosing cholangitis, was simultaneously sought and was negative. Since thyroid disorders are common postpartum and may, although uncommonly, be another aetiology of pruritus, we obtained thyroid function tests which led to the diagnosis of Graves' disease. After starting methimazole, the patient's symptoms improved along with her LFTs. Graves' disease alone may cause severe pruritus, and we considered whether the patient had two, unrelated conditions (cholestasis and Graves' disease). However, given the temporal improvement of both conditions with one medication, we feel the pruritus was most likely caused by Graves'-induced cholestasis.

TREATMENT

The patient was initially treated supportively with emollients and first-generation and second-generation antihistamines. She was then started on ursodiol and later cholestyramine for cholestasis for a total of 2 months, which provided minimal initial relief but ultimately did not relieve her pruritus. After the diagnosis of Graves' disease was made, she was started on methimazole 10 mg/day and endocrinology was consulted. Thyroid function tests (TSH, free T4, T3) were checked every 3 weeks. LFTs were checked every 6–8 weeks to trend and monitor for methimazole-induced hepatotoxicity.

OUTCOME AND FOLLOW-UP

Approximately 4 weeks after starting methimazole, the patient noted significant improvement of her pruritus. AST quickly normalised. Alkaline phosphatase and bile acids trended toward normal approximately 2 months after starting methimazole. It took over 6 months to achieve a euthyroid state. Hepatology was also consulted and helped us complete the cholestasis workup as above, but they did not pursue additional imaging or invasive workup as she was clinically doing very well. Her thyroid and liver function are currently all normal with the exception of alkaline phosphatase, which has trended down to 129 U/L from a peak value of 267 U/L (normal 45–117). She continues to take methimazole 10 mg daily which she is tolerating well. She is considering radioactive iodine (RAI) ablation as she has not reached remission with methimazole.

DISCUSSION

After basic workup revealed two striking abnormalities (cholestasis and hyperthyroidism), we queried whether the two may be either related or causal. In addition to a literature review, we discussed the case with endocrinology and hepatology.

Abnormal liver function tests are occasionally noted in thyroid disease, and thyroid disease may coexist with hepatobiliary

disease. There are two common pathophysiological explanations, which can occur in isolation or in combination.

1. Both thyroid disease and hepatobiliary disease can result from autoimmune disorders. Multiple coexisting autoimmune diseases occur in about 25% of people with autoimmune disease.¹ A salient example of this is primary biliary cholangitis (PBC): 20% of people with PBC have or will develop hypothyroidism, typically in the form of chronic autoimmune (Hashimoto's) thyroiditis.² In these cases, treatment of the two diseases is independent of one another.³
2. Thyroid disease can directly cause damage to the hepatobiliary system. In addition to playing an important role in hepatocyte functioning, thyroid hormones affect bilirubin metabolism, which can lead to increased serum bilirubin via decreased bile flow and bile salt excretion.⁴ This type of direct correlation is more clearly seen in extreme cases of thyroid dysfunction such as thyroid storm, which may cause mild liver dysfunction to fulminant hepatic failure.⁵

Given the lack of evidence of autoimmune liver disease in our case and resolution of hepatobiliary symptoms with treatment of thyroid pathology, we feel it is most likely that this patient's cholestasis was directly caused by her untreated Graves' disease. A growing number of case reports describe cholestasis which resolves with treatment of hyperthyroidism. A 2012 case report discussed a 17-year-old girl presenting with severe cholestasis who was subsequently found to have Graves' disease; treatment with methimazole improved the cholestasis.⁶ Similarly, a 2014 case report described a 52-year-old man with jaundice, pruritus and weight loss found to have Graves' disease and intrahepatic cholestasis.⁷ Several other case studies describe varying manifestations of liver disease associated with Graves' disease.^{8–10}

Several studies discuss the connection between thyroid and liver disease, and 65% of patients with Graves' disease show some degree of hepatic dysfunction.¹¹ Certain risk factors appear to be correlated with increased risk of developing hepatobiliary disease: older age, longer duration of hyperthyroidism and higher level of TRAb.^{11 12}

Antithyroid medications such as methimazole can cause hepatobiliary injury as well, a possible confounding variable when monitoring liver function in patients with hyperthyroidism. Given our patient's relatively mild liver dysfunction and unclear clinical picture, we felt it was reasonable to start with methimazole. However, radioactive iodine (RAI) therapy may be the

Learning points

- Generalised pruritus without a primary rash may signal significant systemic disease and therefore requires a careful history. Initial workup often includes complete blood count, comprehensive metabolic panel, thyroid stimulating hormone level and chest X-ray and HIV testing.
- Hyperthyroidism is frequently associated with some degree of liver dysfunction, which may be symptomatic or asymptomatic.
- Underlying thyroid disease may be treated with standard antithyroid medications such as methimazole or propylthiouracil; alternatively, surgery or radioactive iodine (RAI) may be pursued. Surgery or RAI may be more strongly considered depending on the degree of hepatic dysfunction.
- With appropriate treatment of Graves'-induced cholestasis, most patients do not have long-term liver damage.

preferred treatment in patients with Graves' disease and liver dysfunction.¹¹

Although limited data exists, most patients with Graves'-induced liver injury do not have long-term liver damage. Severity of liver damage, type of liver damage and remission of Graves' disease appear to be the most important factors in long-term hepatobiliary prognosis.¹¹

Contributors JW provided all primary care to the patient. She obtained the patient consent and provided the clinical summary, therapy and results. She also coordinated with the specialists and acquired all records. RMC reviewed the records and discussed the case with JW. She performed literature review, wrote the background, discussion and learning points and edited the case report.

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