

SUCCESSFUL THYROIDECTOMY IN PLUMMER'S DISEASE COMPLICATED BY PROPYLTHIOURACIL-INDUCED CHOLESTATIC JAUNDICE*

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ABSTRACT

Synopsis: Plummer's disease is an unusual cause of thyrotoxicosis in young adults. Remissions do not occur using antithyroid drugs. Radioactive iodine therapy is also not indicated. Surgery is the best option for these patients. Prior to thyroidectomy, patients should be rendered euthyroid using antithyroid drugs to minimize risk of exacerbation of thyrotoxicosis. In a patient who developed a major adverse drug reaction to an antithyroid (i.e. cholestatic jaundice), achieving euthyroidism prior to thyroidectomy is a dilemma to the physicians handling the patient. We therefore present a case of a patient with Plummer's disease who developed cholestatic jaundice due to propylthiouracil (PTU) but successfully underwent thyroidectomy by using propranolol and dexamethasone preoperatively to control thyrotoxicosis.

Clinical Presentation: A 33-year-old, female presented with a three-year history of progressive neck swelling associated with hyperthyroid signs and symptoms.

Physical Findings: There was no exophthalmos. The thyroid was enlarged with multiple, soft, moveable nodules. No bruit was appreciated over the enlarged gland. Cardiac examination was unremarkable. Fine finger tremors were noted.

Laboratory Work-up: Pretreatment thyroid function test results were consistent with thyrotoxicosis. Thyroid ultrasound showed multiple thyroid nodules while the thyroid scan showed hypofunctioning nodules in both lobes.

Diagnosis: Plummer's Disease

Treatment: Patient was given PTU and propranolol. Six weeks after taking PTU, she developed generalized maculopapular, erythematous, pruritic rashes, jaundice, and tea-colored urine. Hyperbilirubinemia was noted while upper abdominal ultrasound and hepatitis titers

were normal. PTU was discontinued and loratadine was given with resolution of rashes and jaundice. She was advised thyroidectomy. Upon admission, patient was biochemically hyperthyroid. Preoperatively, she was given propranolol and dexamethasone for one week.

Outcome: Post-operative course was uneventful.

Significance: This is the first reported case of Plummer's disease who developed cholestatic jaundice to PTU and who subsequently underwent thyroidectomy successfully by using propranolol and dexamethasone preoperatively.

Recommendation: We recommend the use of propranolol and dexamethasone for the rapid preoperative preparation of patients with Plummer's disease prior to thyroidectomy when an antithyroid drug is contraindicated.

Keywords: Plummer's disease, multinodular toxic goiter, PTU-induced cholestatic jaundice, preoperative preparation for thyroidectomy

INTRODUCTION

Plummer's disease (multinodular toxic goiter) is an unusual cause of thyrotoxicosis in young adults. It is more common in those who are more than 50 years old. Depending on the country and iodine intake, patients with multinodular toxic goiter comprise between three and 11 percent of thyrotoxic patients.⁽¹⁾ Spontaneous remissions do not occur. For these patients antithyroid drug is never the treatment of choice except as preparation for treatment with radioactive iodine (RAI) or surgery. Most patients should be treated initially with antithyroid drug to decrease thyroid function quickly and minimize risk of exacerbation during thyroidectomy or after RAI therapy. However for patients who develop major adverse reactions to antithyroid, other drugs should be used to control thyrotoxicosis prior to definitive therapy such as thyroidectomy.

We report a case of a 33-year old Filipino patient with multinodular toxic goiter, and hypofunctioning nodules on thyroid scan, who developed cholestatic hepatitis secondary to PTU. Propranolol and dexamethasone were substituted as preoperative medications and the patient subsequently underwent an uneventful total thyroidectomy.

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CASE REPORT

A 33-year old female presented with a three-year history of progressive swelling in the neck associated with palpitations, hyperdefecation, excessive sweating, easy fatigability, and weight loss despite good appetite. There were no complaints of dyspnea, dysphagia, hoarseness or feeling of suffocation. On examination, there was no exophthalmos. The thyroid was enlarged with 2 x 2 cm, soft, nontender, moveable nodule in the right lobe and 2 x 1 cm, soft, nontender, moveable nodule on the left lobe. There was no bruit appreciated over the enlarged gland. Cardiac rate was normal at 80/min and cardiac rhythm was regular. Fine finger tremors were noted. There was no note of onycholysis and bipedal edema. The patient was hyperreflexic. Her thyroid function tests revealed the following: serum FT4 59.7 pmol/L (NV: 11-24 pmol/L) and serum TSH 0.06 mIU/L (NV: 0.3-3.8 mIU/L). Thyroid ultrasound showed an enlarged thyroid gland with the right lobe measuring 6.1 x 2.2 x 2.3 cm and left lobe measuring 5.8 x 1.7 x 1.3 cm. A solid echogenic nodule measuring 2.5 x 2.5 x 1.8 cm was noted at the upper pole of the right lobe. Two hypoechoic nodules were also seen in the left lobe measuring 1.2 x 0.83 x 0.67 cm and 0.43 x 0.43 x 0.35 cm. Based on her clinical presentation and thyroid function test results the diagnosis of Multinodular Toxic Goiter (Plummer's Disease) was made. PTU 50 mg/tab 2 tabs TID and Propranolol 10 mg/tab 1 tab TID were started.

Six weeks after taking PTU, the patient developed pruritic maculopapular rashes on the trunk and extremities, jaundice, and tea-colored urine. The patient gave no history of hepatitis, alcohol or drug abuse, nor use of herbal medications. She was afebrile. There were no signs of chronic liver disease nor signs of cardiac failure. Abdominal examination was unremarkable. Liver enzymes were slightly elevated: AST 47.51 (NV: 0-46 U/L), ALT 70.95 (NV: 0-49 U/L). Alkaline phosphatase was elevated at 738.55 (NV: 64-306 U/L). There was hyperbilirubinemia: Total bilirubin: 120.02 (NV: 0-25.5mg/dl), Direct bilirubin: 35.87 (NV: 0-8.5 mg/dl), Indirect bilirubin: 84.15 (NV: 0-17 mg/dl). Upper abdominal ultrasound was normal while hepatitis titers were also normal. There was no leukocytosis, nor eosinophilia while the platelet count was normal. Prothrombin time and partial thromboplastin time values were within normal limits. Repeat serum FT4 was already normal at 20 pmol/L. Propylthiouracil was discontinued and loratadine was started for the pruritus and rashes. Thyroid scan was also requested. On follow-up after six weeks, there was resolution of the jaundice and disappearance of the rashes. Liver

function tests returned to normal. Thyroid scan showed multinodular goiter with hypofunctioning nodules in both lobes. The patient was referred to otorlaryngology for thyroidectomy.

The patient failed to undergo thyroidectomy immediately after preoperative clearance was given but instead came back to the Department of Otorhinolaryngology five months later. She was again referred to endocrinology for preoperative clearance. Except for occasional palpitations, the patient did not complain of other hyperthyroid signs and symptoms. Resting heart rate at the time of examination was 84/min. Examination of the neck still revealed thyromegaly with multiple nodules as previously described. The patient however was again biochemically hyperthyroid with a suppressed TSH (0.07 mIU/L) and elevated FT4 (55.3 pmol/L).

Since the patient could no longer be given PTU due to history of cholestatic jaundice, other antithyroid drugs such as methimazole cannot also be given due to reported cases of cross-reactivity with thionamides. Thus, control of thyrotoxicosis was attempted by giving propranolol 40 mg/tab 1 tab TID and dexamethasone 2 mg IV q 6 hrs. for 7 days. Serum FT4 decreased from 55.3 pmol/L to 44.6 pmol/L after one week of treatment. The patient remained clinically euthyroid. Patient was then cleared for total thyroidectomy.

Prior to surgery, the patient received dexamethasone 2 mg IV and propranolol 40 mg/tab 1 tab per orem. Anesthesia was induced using Isoflurane and Fentanyl. Intraoperatively, patient's heart rate ranged from 80's to 90's per minute and the blood pressure remained stable.

Post-operatively, the heart rate varied between 70 beats-80 beats per minute. Propranolol and dexamethasone were continued. Sixteen hours post-op, the patient complained of perioral numbness, tingling sensation, and paresthesias. Chvostek's sign was elicited. Calcium carbonate and calcitriol were started. Dexamethasone was tapered down to twice a day during the second post-op day then to once a day during the third post-op day and subsequently discontinued. Propranolol was also gradually tapered down then discontinued after two weeks. The patient's post-operative course was generally uneventful and she was discharged on the fourth post-op day. Histopathologic finding was consistent with colloid multinodular goiter.

Upon follow-up at the out-patient clinic six weeks post-thyroidectomy, patient complained of cold

intolerance, easy fatigability, and weight gain. The physical examination was essentially unremarkable except for the presence of thyroidectomy scar. Serum FT4 was in the lower range of normal at 11.4 pmol/L (NV: 11-24 pmol/L). Thyroid hormone replacement therapy was then initiated. The patient was also advised lifelong thyroid hormone replacement therapy.

DISCUSSION

Hyperthyroid disease due to multinodular goiter results from autonomous function of nodular thyroid tissue in one dominant or many nodules⁽²⁾. These patients have thyrotoxic signs and symptoms similar to those of Graves' disease but the patients tend to be somewhat older and not to have the ocular or dermatologic stigmata of Graves' disease. Although sharing many common treatment principles, the approach to therapy for these patients differs in certain respects. Radioiodine is the preferred therapy for most patients, although larger therapeutic doses and sometimes multiple treatments are needed⁽³⁾. In this case radioiodine cannot be administered since the patient's thyroid nodules are hypofunctioning, hence are unable to take up radioactive iodine. Moreover, radioiodine cannot reliably reduce the size of the goiter of this patient to a functionally or cosmetically acceptable extent.

Antithyroid drugs such as PTU and methimazole can be used to achieve euthyroidism, however long-term treatment with these drugs in toxic multinodular goiter is not useful because they do not induce disease remission⁽³⁻⁴⁾.

Thus, surgery is the best therapeutic option for this patient with a large multinodular goiter and hypofunctioning nodules on thyroid scan. However, prior to thyroidectomy the patient should be rendered euthyroid by treating initially with antithyroid drug to minimize the risk of exacerbation of thyrotoxicosis during surgery. Preoperative preparation of patients with hyperthyroidism is very crucial to avoid more severe thyrotoxicosis resulting from leakage of thyroid hormone to the circulation at the time of surgery and to decrease intraoperative and post-operative complications related to anesthesia or to the surgical procedure itself. The greatest risk to the perioperative thyrotoxic patient is a thyroid storm, a life-threatening complication that presents with fever, tachycardia, and confusion and may quickly lead to cardiovascular collapse and death. This can occur in the inadequately treated patient during or soon after surgery. In a 10-year review of 36 thyroid storm cases at UP-Philippine General Hospital from 1984 to 1993,

the mortality rate was as high as 14%⁽⁵⁾. Achieving biochemical and clinical euthyroidism prior to thyroidectomy is therefore of utmost importance.

Normally, control of thyrotoxicosis especially in a patient who will undergo thyroidectomy is usually obtained by administering a combination of agents having effects in the thyroid hormone synthetic, secretory and peripheral pathways. Generally, the preference is for initial treatment with a thionamide such as methimazole and PTU if there is sufficient time and there are no contraindications to its use.

Prior to contemplated thyroidectomy control of thyrotoxicosis was attempted in this patient using PTU. Unfortunately the patient developed drug-induced cholestatic hepatitis which resolved after discontinuation of PTU. As of date there is no reported case of cholestatic hepatitis due to PTU. PTU is notable for causing hepatocellular injury which is generally more severe, associated with marked elevation of serum aminotransferase levels up to more than six times the upper limit of normal, and hepatic necrosis on biopsy,^(4, 17-20) which were not noted in our case. The average duration of PTU therapy before the onset of hepatotoxicity is approximately three months,⁽⁴⁾ while our patient presented with the above-mentioned manifestations only six weeks after initiation of PTU. Cholestasis occurs exclusively with methimazole and carbimazole as reported in the literature.^(6-7,21-28)

The mechanisms of cholestasis can be broadly classified into intrahepatic, where an impairment of bile formation occurs, and extrahepatic, where impedance to bile flow occurs after it is formed. Intrahepatic cholestasis occurs in certain instances of viral, alcoholic, drug-induced, and chronic liver disease. Gallstones, bile duct strictures, and tumors are the most frequent causes of extrahepatic (mechanical) bile duct obstruction. Cholestatic liver disease is characterized by a predominant elevation of serum alkaline phosphatase and bilirubin⁽²⁹⁾ as was seen in our patient.

Our patient fulfilled the definition and criteria for cholestatic drug-induced liver disease, as established by the International Consensus Meeting for liver injury.⁽³⁰⁾ In addition, the patient also fulfilled the diagnostic criteria of drug-induced hepatotoxicity as proposed by Hanson in 1984 which includes the following: clinical and laboratory evidence of hepatocellular dysfunction; onset of symptoms temporally related to drug therapy; no serologic evidence for current infection with hepatitis A or B; absence of an acute hepatic insult such as shock

or sepsis; no evidence of chronic liver disease; and absence of other concomitantly administered drugs, especially known hepatotoxins. The presence of rash in our patient is also supportive of drug-induced hepatotoxicity. The chronologic relationship between drug ingestion, onset, and resolution of liver injury is the most important factor in diagnosis of drug-induced cholestatic liver disease. The course of the reaction after discontinuing the drug and the response to readministering the drug are also helpful in the diagnosis.⁽³¹⁻³²⁾

In this case, cholestatic hepatitis was most likely caused by PTU. First and foremost, chronologic relationship between the initiation of PTU and development of cholestatic hepatitis was clear. Second, jaundice and liver function tests returned to normal after drug withdrawal. Third, concomitant risk factors for liver injury were excluded by history, physical examination, and serological tests. Fourth, hyperthyroidism is an unlikely cause of our patient's cholestatic hepatitis since our patient's serum FT4 was already normal at the time of presentation. Cholestasis due to hyperthyroidism usually occurs in association with marked elevation of plasma levels of thyroid hormones.⁽²⁵⁾ Fifth, cholestasis secondary to propranolol which was also taken by the patient along with PTU has not been reported in the literature.

Substitution with another antithyroid such as methimazole was not attempted in this case because aside from the known fact that methimazole can cause cholestatic hepatitis, cross-reactivity with PTU has been reported.⁽⁸⁾ Cross-reactivity between the two agents is as high as 50%.⁽⁴⁾

Patients with major side effects to antithyroid such as cholestatic jaundice in whom antithyroid drug therapy is discontinued usually become thyrotoxic soon thereafter, if they were not thyrotoxic when the drug was discontinued just as what happened in this patient. Five months after she was cleared for surgery the patient was again biochemically hyperthyroid. In this patient where antithyroid drug therapy is no longer an option, alternative drugs should be used to control thyrotoxicosis. Inorganic iodide, iodinated radiographic contrast agents, lithium carbonate, corticosteroids, and beta-adrenergic blockers are among of the alternative agents that could be used to control thyrotoxicosis.⁽¹⁴⁾

Iodide cannot be given in this case since in patients with toxic multinodular goiter it can worsen symptoms and increase serum T4 and T3 concentrations, especially if the patient's iodine intake was marginal.⁽¹⁾ Because iodide can provide

substrate for thyroid hormone synthesis through the Jod-Basedow effect⁽⁹⁾, it is usually used in combination with antithyroid drugs which we can no longer do in this case. Iodinated radiographic contrast agents cannot also be used in the preoperative preparation of this patient since these can exacerbate hyperthyroidism if thyroid hormone production is not first blocked by the administration of a thionamide as in our case. Although lithium carbonate impairs release of thyroid hormone and has been used in the treatment of hyperthyroidism, it is associated with significant toxicities and experience with its use in thyrotoxicosis is limited⁽⁹⁾.

We are therefore left with beta-blockers and corticosteroids to prepare our patient preoperatively. Beta-blockers were first used in the preoperative preparation of thyrotoxic patients within a few years of propranolol's introduction in 1964. Though propranolol was the first agent used in this class, others, both longer acting (eg, atenolol) and shorter-acting (eg, esmolol) have also been used successfully usually in patients with Graves' disease.⁽¹⁰⁻¹²⁾ Literature review (both local and international) did not reveal any published case reports or series emphasizing use of beta-blockers in the preoperative preparation of patients with Plummer's disease. All of those reported in the literature dealt mainly with thyrotoxicosis secondary to Graves' disease. Beta-blockers as a class reduce many of the symptoms of thyrotoxicosis, especially those related to the cardiovascular system. Beta-blockers do not impact on the production of thyroid hormone, so hyperthyroid patients continue to have biochemical hyperthyroidism even as symptoms improve. Propranolol at high doses (120 – 320 mg/d) have some impact on the peripheral conversion of T4 to T3, which is not seen in other agents like atenolol, but the clinical significance of this is small.⁽¹³⁾ Thus, propranolol is rarely used alone in the preoperative preparation of a thyrotoxic patient.

Corticosteroids such as dexamethasone (2 mg per orem or IV q 6 hours), betamethasone (0.5 mg po q 6 hours, IM or IV) and hydrocortisone (100 mg po or IV q 8 hours) can decrease peripheral conversion of T4 to T3 thus are also used in the preoperative preparation of thyrotoxic patients in combination with antithyroid and other above-mentioned agents (i.e. beta-blockers).^(9,14) As of date, there is no published case report on the use of dexamethasone alone in the perioperative preparation for thyroidectomy of a thyrotoxic patient. Most of the cases reported in the literature used a combination of either antithyroid, beta-adrenergic agent, iodinated contrast agents, or iodide.^(9,14)

For patients undergoing thyroidectomy, the removal of the thyroid gland does not result in immediate resolution of thyrotoxicosis since circulating half-life of T₄ is about seven to eight days. Therefore some agents of the preoperative regimen may need to be continued for several days after surgery. As thyroid hormone levels decrease, these agents can be gradually removed. In patients who were rendered euthyroid before surgery beta-blockers can often be weaned off during the first two weeks after surgery.⁽⁹⁾ In our case propranolol was gradually decreased after one week, then discontinued two weeks postoperatively. On the other hand, dexamethasone was given for one week then tapered down 72 hours post-operatively.

Extensive review of the literature both locally and abroad did not show any similar case (Plummer's disease) successfully managed with both propranolol and dexamethasone perioperatively since most of the published literatures dealt mainly with the rapid perioperative preparation of patients with Graves' disease.⁽⁹⁻¹³⁾ Thus this is the first reported case of Plummer's disease complicated by PTU-induced cholestatic jaundice who successfully underwent thyroidectomy using readily available medications such as propranolol and dexamethasone.

Our patient came back six weeks post-total thyroidectomy clinically and biochemically hypothyroid. Considering the initial treatment only, the actuarial probability of developing hypothyroidism at one year was 16 percent after thyroidectomy.⁽¹⁵⁾ Patients treated surgically continue to have slight increase in probability of being discovered to be hypothyroid with continued follow-up (26% at 10 years).⁽¹⁶⁾ Lifetime thyroid hormone replacement therapy is therefore warranted as was given to this patient.

CONCLUSION

Cholestatic hepatitis can also occur with propylthiouracil and therapy consists of immediate cessation of the said offending agent. Preoperative preparation for Plummer's disease complicated by a major adverse reaction to antithyroid such as cholestatic hepatitis can be rapidly and successfully accomplished by the simultaneous administration of propranolol and dexamethasone.

RECOMMENDATION

Based on our experience with this patient, we recommend that the use of propranolol and

dexamethasone should be considered for the rapid preoperative preparation of patients with multinodular toxic goiter prior to thyroidectomy when antithyroid is contraindicated. Moreover, physicians and patients should be made aware that PTU-induced cholestatic hepatitis exists such that upon occurrence of the said condition, PTU can be immediately discontinued and unnecessary procedures are avoided.

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