A Case of Thyrotoxic Periodic Paralysis and Graves' Ophthalmopathy Patient in Coincidence with Chronic Hepatitis B Infection

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ABSTRACT

Graves' disease is an autoimmune thyroid disease with several characteristic symptoms and signs. Graves' ophthalmopathy, an inflammatory disease in the orbital area, is the main extrathyroid manifestation of Graves' disease. About 5% of Graves' ophthalmopathy patients have moderate to severe severity requiring high doses of systemic corticosteroid therapy. Graves' disease also has few complications, one of which is thyrotoxic periodic paralytic characterized by hypokalemia and muscle paralysis. Chronic hepatitis B virus infection has the potential to be co-incidence with other diseases (eg Graves ophthalmopathy). The need of high dose of corticosteroid therapy in treating Graves' ophthalmopathy is a risk of reactivation in hepatitis B infection patient. This paper presented a Graves' disease patient complicated with Graves' ophthalmopathy who developed limb muscle weakness. Patient will receive high doses of corticosteroids and prophylactic lamivudine therapy to prevent hepatitis B virus reactivation.

Keywords: *Graves disease, thyrotoxic periodic paralysis, Graves ophthalmopathy, hepatitis B reactivation*

ABSTRAK

Penyakit Graves merupakan penyakit tiroid autoimun dengan beberapa gejala dan tanda yang khas, salah satunya adalah Graves Oftalmopati, suatu penyakit inflamatori di daerah orbita yang menjadi manifestasi ekstratiroid utama penyakit Graves. Sekitar 5% pasien Graves Oftalmopati memiliki tingkat keparahan sedang hingga berat yang memerlukan terapi kortiksteroid sistemik dosis tinggi. Penyakit Graves juga memiliki komplikasi, salah satunya adalah tirotoksikosis periodik paralisis yang ditandai dengan hipokalemia dan paralisis otot. Infeksi kronis virus hepatitis B berpotensi koinsiden dengan penyakit lain (mis. Graves oftalmopati) sehingga berisiko mengalami reaktivasi bila mendapatkan terapi kortikosteroid dosis tinggi. Kami melaporkan seorang pasien dengan penyakit Graves dalam terapi antitiroid yang mengalami kelemahan otot ekstremitas. Pasien juga terdiagnosis Graves oftalmopati yang akan mendapat kortikosteroid dosis tinggi. Pasien memiliki HBsAg yang positif saat skrining, sehingga diberi terapi profilaksis lamivudin untuk mencegah terjadinya reaktivasi virus hepatitis B akibat efek imunosupresif kortikosteroid dosis tinggi. Pasien diijinkan untuk pulang berobat jalan dengan perbaikan kondisi.

Kata kunci: *penyakit Graves, tirotoksikosis periodik paralisis, oftalmopati Graves, reaktivasi hepatitis B*

INTRODUCTION

Graves' disease is an autoimmune disease characterized by the present of autoantibodies of thyroid-stimulating hormone (TSH) receptor causing hyperthyroidism. One of the complications that can occur in patients with Graves' disease is thyrotoxic periodic paralysis.[1] Thyrotoxic periodic paralysis (TPP) itself is a disorder characterized by sudden hypokalemia and paralysis. This condition mainly affects the lower extremities and is secondary to thyrotoxicosis, especially in the hyperthyroid state caused by Graves' disease.[2] About 20 to 25 percent of Graves' disease patients have clinical features of Graves orbitopathy (ophthalmopathy).[3] Graves ophthalmophathy (GO) is an eye disorder which is the main extrathyroid manifestation of Graves' disease resulting from thyroid dysfunction. Intravenous high-dose corticosteroid is the initial treatment for moderate to severe active Graves' ophthalmopathy disease.[4]

Chronic hepatitis B virus (HBV) infection is a major health problem affecting approximately 350 to 400 million people worldwide.[5] Patients with chronic HBV infection are at risk of experiencing HBV reactivation if they receive chemotherapy, immunosuppressants, or high dose corticosteroids. Hepatitis B virus reactivation can be asymptomatic, causing mild symptoms, or causing severe conditions like hepatocellular damage, liver failure, or death.[6]

The key to preventing HBV reactivation is identification of patients with HBV infection and provide prophylactic antiviral therapy in patients who are at high risk.[6] The following is a case report of a patient with Graves' disease complicated with thyrotoxic periodic paralysis and Grave's ophthalmopathy receiving high-dose corticosteroid therapy in coincidence of chronic hepatitis B infection.

CASE ILLUSTRATION

A man, 32 years old came to the emergency room of Dr. Soetomo General Hospital with a chief complaints of lower limb weakness in April 2018. The patient complained about having lower limb weakness that felt suddenly in 4 hours before entering the emergency room. Patient had started to complain that the limbs were difficult to move before but still able to walk. Similar symptoms happened in January and December 2017, but got better on the next day without therapy.

Patient also complained about having pain in the back of both eyes since 3 months ago, especially aggravated by moving the eyes. Besides that, patient complained of swollen eyelids, red eyes and double vision. He was planned to receive 750 mg intravenous methylprednisolone injection once a week for 6 weeks. He denied any shortness of breath, slurred speech, headache, vomiting, fainting, fever and cough. There is increasing of appetite with a frequency of 4-5 times a day. There are no complaints of defecating and urinating.

The patient was diagnosed with Grave's disease since March 2018 and received thyrozol 10mg daily and propranolol 10 mg daily. There's no history of diabetes mellitus and hypertension. He had tattooed his hands in 2017. History of intravenous drug user, free sex, and got transfusions were denied. Patient works as a construction worker. Patient smoked since ± 10 years ago. From physical examination, we found general condition of weakness with GCS 456. His body weight was 65 kg and 165 cm in height. Blood pressure 130/80 mmHg, pulse 96x/minute regular rhythm, breaths 20x/minute, and axillary temperature 36.7^{o}C.

From the head and neck examination, exophthalmus, Stellwag Sign, Dalrymple's Sign were found. There were no conjungtiva pallor, jaundice sclera, or cyanosis. Cavities and signs of infection in the nose, ears, throat, sinuses, and enlarged lymph nodes weren't found. Right-left eye vision was 5/6 and 6/60, right-left intraocular pressure both were 17.6, with proptosis, palpebral edema and hyperemic conjunctiva. Funduscopy examination found normal. A diffuse thyroid enlargement of 3x4x2 cm was found, fixed, supple consistency, and no pain in palpation. There's no thrill or bruit on auscultation.

From chest examination, we obtained symmetrical shape, symmetrical movements, no intercostal or supraclavicular retraction. Cardiac examination obtained a single S1 and S2, regular without addition heart sounds, no gallop rhythm, or pericardial scraping sound. Examination of the lungs revealed vesicular breath sounds in both hemithorax, no crackling or wheezing in both lung fields.

From abdominal examination, we obtained a flat abdomen with normal bowel sounds. There was no collateral vein dilation, medusa head, organomegaly. There is no tenderness in all areas of the abdomen.

From extremities examination, the acral limb is warm, dry, and looked red. There was a motor neurological deficit with a muscle strength value of 4 in all four extremities, but no pathological reflex or sensory deficits. There is no enlarged lymph nodes in the armpits and groin. There were no petechiae, pustules, bullae, squama and rash, with normal skin

turgor. From laboratory examination, we found Hb 15.0 g/dL, Hct 45.2%, leukocytes 9,170/mm^3, platelets of 254,000/mm^3, neutrophils 66.3%, random blood sugar 198 mg/dL, serum creatinine 0.75 mg/dL, BUN 9 mg/dL, 4.27 g/dL albumin, 27 U/L AST 29 U/L ALT, Potassium 2.2 mmol/L, sodium 141 mmol/L sodium, chloride 107 mmol/L, and reactive HbsAg. From electrocardiography examination, we found sinus rhythm with heart rate 97x/minute, normal axis and AV block grade 2 type 1. From radiology examination of AP Chest X-ray we found within normal limits.

Based on the history taking, physical and supporting examinations, the patient was diagnosed with thyrotoxic periodic paralysis (TPP) with differential diagnosis of Familial Hypokalemia Periodic Paralysis, Grave's Ophthalmopathy, and Hepatitis B. Patient is planned for laboratory examination such as urine electrolyte, anti HCV, HBeAg, anti HBe, VHB DNA, serum electrolyte post correction, FT4, and TSH. Patient is also planned for fibroscan examination and serial ECG. Patient is given 2100 kcal/day with low-carbohydrate high-protein diet, KN2 infusion 1,000 mL for 24 hours, Thyrozol 10 mg for every 24 hours, Propranolol 20 mg for every 8 hours, and KSR tablet every 12 hours.

On 2nd day of treatment, the weakness of the lower limbs has improved as patient able to walk around the bed. There is no palpating, nausea and vomiting. BP 130/70, regular HR 86x/minute, RR 18x/minute, and axillary temperature 36.8^{o}C. The laboratory results were negative for anti HCV, sodium 142 mmol/L, potassium 4.4 mmol/L, chloride 106 mmol/L, calcium 8.7 mg/dL, phosphate 3.5 mg/dL, magnesium 2.1 mg/dL. Urine electrolytes obtained urine potassium 60 mmol/24 hours, urine sodium 216 mmol/24 hours, and urine chloride 252 mmol/24 hours. The total T3 was 1.71 ng/mL, FT4 was 1.94 ng/dL, and TSH was 0.005 uIU/ mL. The results of blood gas analysis were Ph 7.42, PO2 82, PCO2 40, HCO3 22.5, BE 1.4, SpO2 96%.

Patient diagnosed with Thyrotoxic periodic paralysis, Hepatitis B, and Graves ophthalmopathy. He was consulted to ophthalmologist, endocrinologist, and gastroenterologist. Ophthalmologist advised to give the patient 750 mg methylprednisolone injection weekly for 6 times and continued with 500 mg weekly for 6 times. Endocrinologist advised low carbohydrate high protein diet and correction of potassium maximum 50 meq/24 hours. Propranolol was planned to be discontinue if the EKG sinus rhythm. Gastroenterologist gave the patien Lamivudine 1x100 mg and planned to check HBV DNA and HBeAg.

On the 3rd day of treatment, the condition improves, the patient can do activities as usual, and the chest is not palpitating. BP 120/70, regular HR 88x/minute, RR 18x/minute, and axillary temperature 36.8^{o}C. Laboratory results of sodium 135 mmol/L, potassium 4.1 mmol/L, chloride 104 mmol/L. Patients were allowed to go home with lamivudine therapy 1x100 mg, thyrozol 1x10 mg, education to reduce carbohydrates while eating, as well as routine control to gastroenterohepatology, endocrine and eye clinic.

One week later when the control at the patient's gastro clinic was performed a fibroscan examination with results according to F0-F1.

DISCUSSION

Graves' disease is an autoimmune disease that consists of hyperthyroidism, goiter, eye disease (orbitopathy), and sometimes a dermopathy called pretibial (localized) myxedema. Hyperthyroidism is the most common feature of Graves' disease. This disease is caused by the thyrotrophin receptor antibody (TRAb) which activates the thyrotropin (TSH) receptor, thereby stimulating the synthesis and secretion of thyroid hormones, as well as thyroid growth which cause diffuse goiter. The presence of TRAb in serum and orbitopathy can differentiate Graves' disease from other causes of hyperthyroidism.[7]

General signs and symptoms are caused by hyperthyroidism. Few signs and symptoms such as anxiety, emotional lability, weakness, tremors, palpitations, heat intolerance, excessive sweating, weight loss, hyperdefecation, menstrual disorders, tachycardia, fine tremor, skin feels warm and wet, thin hair and loss, and periodic paralysis are due to hypermetabolic condition. Typical signs and symptoms of Graves' disease are diffuse enlarged goiter, ophthalmopathy, dermopathy, and thyroid acropachy.[1]

The diagnosis can be made if there are signs and symptoms of hyperthyroidism accompanied by typical signs and symptoms of Graves' disease. Even the sign and symptoms are less clear, definite biochemistry showing hyperthyroidism conditions such as increase in FT4 with low TSH levels can be reason for diagnosis.[1, 8]

Symptom control is the main purpose in treating Graves' disease. Beta blockers should be started soon after diagnosis of hyperthyroidism, if there are no contraindications, even before confirmation that the cause of hyperthyroidism is Graves' disease. All beta blocker drugs are effective in reducing symptoms

of hyperthyroidism and are given until a euthyroid condition.[7]

Antithyroid drugs, radioiodine ablation, or thyroidectomy can effectively decrease thyroid hormone synthesis. There is no consensus on the best treatment option. American Thyroid Association (ATA) guidelines emphasize discussing treatment options with patients and considering their preferences before deciding on treatment. Methimazole is the main drug used for Graves' hyperthyroidism. Methimazole has a faster efficacy, longer duration of action and can be given once a day.[7, 9]

The patient presents with palpitations, frequent sweating, and frequent shaking which are common symptoms of hyperthyroidism. Beside that, there are signs and symptoms of Graves' disease such as diffuse enlarged adenoids and ophthalmopathy obtained from patient. Laboratory tests showed an increase in FT4 and a decrease in TSH levels (FT4 1.94 ng/dL, and TSH 0.005 uIU/mL). These signs and symptoms are consistent with Graves' disease. The patient received thyrozol 10 mg and propranolol 10 mg daily.

Thyrotoxic periodic paralysis (TPP) is a rare but potentially fatal complication of hyperthyroidism characterized by the TPP triad that consists of acute hypokalemia without a total body potassium deficit, reversible muscle paralysis, and thyrotoxicosis. This condition mainly affects young Asian men in the age group of 20-40 years with the male to female ratio ranging from 17:1 to 70:1.[10,11]

Typical attacks of TPP are characterized by episodes of transient muscle weakness, ranging from mild weakness to total flaccid paralysis and generally involving the lower limbs then progressing to the upper limbs. Decreased muscle tone, tendon reflexes, and areflexia may occasionally occur. Sensory nervous system, bowel and bladder functions are not affected. Patients generally experience complete recovery between episodes of muscle weakness. Thyrotoxic periodic paralysis attacks only occur during hyperthyroidism and do not occur when thyroid hormones are normal. The severity of muscle weakness generally corresponds to the degree of hypokalemia. Familial hypokalemic periodic paralysis (FHPP) has same symptoms but without evidence of hyperthyroidism.[10,12]

Thyrotoxic periodic paralysis (TPP) attacks are generally triggered by any conditions that increase insulin release. The increase in insulin causes potassium to enter the cells which in turn causes hypokalemia. Hypokalemia is not caused by a potassium deficiency, and is not associated with urinary potassium loss, due to normal or low urinary potassium excretion, and normal blood acid-base balance. This intracellular shift is due to increased activity of the Na/K-ATPase pump. High circulating thyroid hormone levels in hyperthyroidism, adrenergic responses associated with hyperthyroidism, and androgens can increase Na/K-ATPase activity. A high carbohydrate diet, high salt intake, trauma, strenuous exercise, exposure to cold, and alcohol consumption are some of other trigger factors. Some drugs such as diuretics, estrogens, and laxatives can also trigger TPP.[2,10,12]

Typical ECG findings on TPP include sinus tachycardia, increased QRS voltage, PR interval abnormalities, and grade 1 AV block.[12,13]

Thyrotoxic periodic paralysis treatment has two main objectives, namely prompt correction of hypokalemia and definitive therapy of hyperthyroidism to prevent further attacks. Immediate correction of hypokalemia aims to prevent life-threatening cardiopulmonary complications and speed recovery of muscle weakness. Treatment with oral or intravenous potassium chloride (KCl) will help relieve attacks of acute paralysis. Doses can vary from 50 to 200 mmol and should be infused slowly, unless there are cardiovascular complications. Rebound hyperkalemia can occur especially if more than 90 mEq KCl is given in the first 24 hours. Patients receiving KCl $\leq$ 50 mEq rarely develop rebound hyperkalemia. Monitoring serum potassium levels should be done frequently to prevent rebound hyperkalemia. In general, paralysis will improve within 3-36 hours after the initial administration of potassium therapy. Potassium supplementation does not play a role in preventing attacks of paralysis so it cannot be given between attacks. Non-selective beta blockers such as propranolol (oral or intravenous) can reduce Na/K-ATPase activity, so it can be given during acute attacks and can prevent recurrent attacks. This drug is given at a dose of 20-80 mg every eight hours. TPP will resolve if euthyroid condition is achieved, so definitive therapy of hyperthyroidism with radioiodine ablation or thyroidectomy is also a treatment option for TPP.[2,10,11,12]

This patient has a triad of TPP which includes hypokalemia, muscle weakness, and thyrotoxicosis. He has history of previous TPP attacks with complete recovery. TPP attacks occur in conditions of hyperthyroidism (increased levels of FT4). The trigger for TPP attacks in this patient is a high carbohydrate diet. Urine potassium values and blood gas analysis were within normal limits. ECG results show sinus

tachycardia and abnormal PR interval. This patient received an infusion of KCl ≤ 50 mEq per day and propranolol 20 mg every 8 hours orally on a low carbohydrate diet.

Graves' ophthalmopathy (GO) is an inflammatory eye disease that develops in the orbit and is associated with autoimmune thyroid disorders. In the majority of cases (± 90%), GO occurred in patients with current or past Graves' disease. About one third of patients with Graves' hyperthyroidism have some signs and/or symptoms of GO, and only 5% have moderate to severe GO disease.[9]

Most patients with GO show mild signs and symptoms such as corneal irritation, periocular swelling, lid retraction, chemosis/conjunctival erythema, and extraocular muscle dysfunction. A small proportion of patients (about 5%) develop severe symptoms, such as severe inflammation/congestion, excessive proptosis, and vision-threatening corneal ulcers or optic neuropathy. Another study states that the incidence of optic nerve neuropathy that threatens blindness is less than 2%.[14]

Several risk factors such as genetics, smoking, thyroid dysfunction, radioactive iodine, and TRAb can affect the development or progression of GO. Research shows that antithyroid drugs or thyroidectomy do not affect GO progression, but radioactive iodine (RAI) has a small but significant risk of worsening active GO. Patients with inactive GO can be treated with RAI without an increased risk. Smoking is the strongest and most consistent risk factor for GO progression and has a worse response to therapy.[3,14]

Typical signs of GO are marked stare, proptosis, conjunctival inflammation and periorbital edema. In general, direct diagnosis is made in thyrotoxicosis patients with bilateral proptosis without the need for additional laboratory or imaging data.[3,14]

Proper management of GO is based on accurate determination of disease severity (degree of ocular dysfunction or involvement) and clinical activity (degree of active inflammation). The severity can be classified as mild to vision threatening level (Table 1).

GO activity can be assessed using a clinical activity score (CAS) which is useful for determining therapy and predicting response to anti-inflammatory therapy. Each visible clinical symptom equals one point of CAS score (Table 2). CAS scores ≥ 3 out of 7 are classified as having active disease and this condition tends to respond to corticosteroid therapy.[3, 14]

Patients with GO are treated according to the severity of the disease. Treatment of GO patients includes management of hyperthyroidism (if any), smoking cessation, local therapy to reduce eye irritation, and reduce inflammation of the periorbital tissue. Most patients with mild and moderate ophthalmopathy generally improve spontaneously and require only simple management. Mild ophthalmopathy conditions can be treated by thionamide, radioiodine,

Table 1. Graves ophthalmophathy (GO) severity assessment[14]

GO severity assessment						
Degree of severity	**Lid retraction**	**Soft tissue involvement Proptosis**	**Proptosis[a]**	**Diplopia**	**Corneal exposure**	**Optic nerve status**
Mild (≥ 1 of following)	< 2 mm	mild	< 3 mm	Transient[b] or absent	Absent	Normal
Moderate to severe (≥ of following)	≥ 2 mm	Moderate or severe	≥ 3 mm	Inconstant[b] or constant	Mild	Normal
Sight threatening (1 of last 2 categories)	Not contributory	Not contributory	Not contributory	Not contributory	Ulceration	Compromised

[a] Proptosis refers to the variation compared with the norm for each race or to the patient's baseline if available

[b] Intermittent diplopia: present when the patient is fatigued; inconstant diplopia: present at extremes of gaze; constant diplopia: present in primary gaze

Table 2. Assessment of Graves' orbitopathy: clinical activity score elements[1,2]

Elements*	Each visit	Comparison with previous visit	score
Painful feeling behind the globe over last four weeks	x		1
Pain with eye movement during last four weeks	x		1
Redness of the eyelids	x		1
Redness of the conjunctiva	x		1
Swelling of the eyelids	x		1
Chemosis (edema of the conjunctiva)	x		1
Swollen caruncle (flesh body at medial angle of eye)	x		1
Increase in poptosis ≥ 2 mm		x	1
Decreased eye movements ≥ 5º any direction		x	1
Decreased visual acuity ≥ 1 line on Snellen chart		x	1

GO: Graves'orbitopathy, CAS: clinical activity score

A seven-point scale (excluding the last three elements) is used when no previous assessment is available. GO is considered active in patients with a CAS ≥ 3

and thyroidectomy therapy. Some authors suggest six months therapy of selenium for patients with mild ophthalmopathy. Selenium can improve soft tissue swelling in certain patients. For moderate/severe to vision threatening ophthalmopathy, radioiodine is a contraindication as it worsening the condition. Severe ophthalmopathy is characterized by worsening diplopia, exposure keratitis and/or optic neuropathy causing visual disturbances. Severe ophthalmopathy requires treatment such as steroids, orbital decompression, or radiotherapy.[1,15] High-dose systemic glucocorticoid is the first-line treatment for moderate-severe and active GO. Intravenous glucocorticoid is more effective than oral glucocorticoids. An intermediate dose regimen of methylprednisolone with an initial dose of 0.5 g once a week for 6 weeks, followed by 0.25 g once a week for 6 weeks (cumulative dose 4.5 g) is recommended in most cases of moderate-severe and active GO. A high-dose regimen with an initial dose of 0.75 g once a week for 6 weeks, followed by 0.5 g once a week for 6 weeks (cumulative dose 7.5 g) is given for the worst cases in the moderate to severe spectrum. Researchers recommend that the cumulative dose of intravenous glucocorticoids should not be more than 8 g.[4]

In this patient, Graves' disease was complicated by GO with severe symptoms, which is excessive proptosis. Some of the risk factors that can affect the progression of GO in patients are smoking and hyperthyroidism. CAS score in this patient was ≥ 3 out of 7 and classified as active disease with moderate-severe degree. The patient received high-dose methylprednisolone at an initial dose of 0.75 g once a week for 6 weeks, followed by 0.5 g once a week for 6 weeks.

Hepatitis B virus (HBV) is a preventable viral infection. Almost 2 billion people worldwide are infected with this virus. HBV reactivation can occur in patients with chronic or past HBV infection. Patients with chronic HBV infection are at risk of reactivation when using immunosuppressive therapies such as chemotherapy, immunosuppressants, anti-CD20 antibodies, TNF inhibitors, or corticosteroids.[6,16]

Hepatitis B virus reactivation is the re-emergence of active necro-inflammatory disease. This condition is characterized by a 1.5-2-fold increase in ALT and viral load DNA more than 2000 IU/mL in inactive hepatitis B carrier, or in patient who become HBV DNA positive after previously diagnosed as having resolved hepatitis B infection.[16]

Hepatitis B virus reactivation can be mediated through suppression of immune control or direct stimulation of glucocorticoid responsive elements in the HBV genome. Reactivation can occur in patients who receive corticosteroids alone. The key to preventing HBV reactivation is the identification of patients with HBV infection before giving immunosuppressive therapy. Prophylactic antiviral therapy is recommended for patients with moderate and high risk. For low-risk patients, close monitoring is needed and antiviral therapy can be started immediately if first sign of HBV reactivation is detected.[6]

The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines recommend pre-emptive therapy for HBsAg carriers who are about to initiate immunosuppressive therapy, including steroid monotherapy. Steroid doses equivalent to prednisone 2 mg/kg body weight or more than 20 mg/day and consumed for more than two weeks is defined as immunosuppressive therapy, so prophylactic treatment should be considered. Low dose of steroid given less than two weeks do not require prophylaxis. Prophylactic treatment is given 1 to 3 weeks before immunosuppressive therapy started and continued for 6 months to 1 year after discontinuation of therapy. Patients with occult or resolved hepatitis have a lower risk of reactivation so prophylaxis is not required.[16, 17]

Hwang and the American Gastroenterological Association (AGA) recommend prophylactic antiviral therapy for patients at high risk of HBV reactivation. For patients with moderate risk, prophylactic therapy or delayed with initial close monitoring can be considered. Pre-emptive antiviral therapy is started if signs of HBV reactivation are found at monitoring. Low-risk patients do not require prophylaxis unless there are sign of reactivation (Table 3).[6, 18]

The evidence regarding choosing the right antivirus is still limited. Lamivudine is the drug most commonly used and has been shown to reduce the risk of reactivation, mortality and morbidity. Given the high resistance to lamivudine, it is advisable to give other antivirals with higher genetic barrier to resistance. Entecavir and tenofovir are relatively safe options and have great potential with low resistance for long-term immunosuppressant treatment.[16,19]

This patient presents with graves ophthalmopathy which requires very high doses of corticosteroids. High doses of corticosteroids therapy will cause immunosuppression which is a high-risk factor of HBV reactivation. The patient had positive HBsAg and given prophylactic therapy with lamivudine 1x100 mg to prevent HBV reactivation.

Table 3. Risk stratification of hepatitis B reactivation[6,18]

Risk level	Positive HBsAg	Negative HBsAg and positive anti-HBc	antiviral therapy
High risk	1. Chemotherapy 2. Anthracycline class (doxorubicin, epirubicin) 3. B cell-depleting agents, such as anti-CD20 (rituximab, ofatumab) 4. Immunosuppressive therapy for transplantation 5. Steroid therapy combined with other immunosuppressive therapy 6. Moderate and High-dose steroid therapy for more than 4 weeks. Moderate dose equivalent as 10-20 mg prednisone and high dose equivalent as >20 mg prednisone	1. Chemotherapy for hematologic malignancy 2. B-cell depleting agents 3. Anti-CD52	Prophylactic therapy
Moderate risk	1. TNF-α inhibitor (etanercept, adalimumab, certolizumab, infliximab) 2. Cytokine inhibitor or other integrin inhibitor (abatacept, ustekinumab, natalizumab, vedolizumab) 3. Tyrosine kinase inhibitor (imatinib, nilotinib) 4. Other immunosuppressive therapy without steroid (azathioprine, 6-mercaptopurine, methotrexate) 5. Low dose steroid (< 10 mg prednisone) for more than 4 weeks	1. Chemotherapy for solid tumour 2. Anthracycline class 3. Cytokine inhibitor or other integrin inhibitor 4. Tyrosine kinase inhibitor 5. Immunosuppressive therapy for transplantation 6. Steroid therapy combined with other immunosuppressive 7. Moderate and High-dose steroid therapy for more than 4 weeks.	Consider prophylactic therapy or pre-emptive therapy
Low risk	Any dose of steroid therapy less than 1 week	1. TNF-α inhibitor 2. Other immunosuppressive therapy without steroid 3. Low dose steroid for more than 4 weeks 4. Any dose of steroid therapy less than 1 week	No need for prophylactic therapy, pre-emptive therapy only if there's sign of reactivation

A case of Graves' disease with Graves' ophthalmopathy has been reported in patient with hepatitis B infection. The patient had sudden muscle weakness in all four extremities and hypokalemia as a complication of Graves' disease diagnosed with thyrotoxic periodic paralysis. The patient is also diagnosed with Graves' ophthalmopathy and will receive a high dose of methylprednisolone injection at a cumulative dose of 7.5 grams for 12 weeks. Administration of high doses of corticosteroids can cause immunosuppression. Patient was HBsAg positive and receiving high-dose steroid make this patient as high-risk of reactivation, so he was given prophylactic lamivudine therapy to prevent HBV reactivation.

REFERENCES

1. Sutjahjo A, Wironegoro R, Novida H. Penyakit graves (graves disease). In: Tjokroprawiro A, Setiawan PB, Effendi C, Santoso D, Soegiarto G, editors. Buku ajar ilmu penyakit dalam. Edisi-2. Surabaya: Airlangga University Press (AUP); 2015.p.126-133.
2. Vijayakumar A, Ashwath G, Thimmappa D. Thyrotoxic periodic paralysis: clinical challenges. Journal of thyroid research, 2014.
3. Davies TF, Burch HB. Clinical features and diagnosis of Graves' orbitopathy (ophthalmopathy) [serial online]. Uptodate, 2019 [cited 20 October 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-graves-orbitopathy-ophthalmopathy.
4. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European thyroid association/ European group on Graves' Orbitopathy guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J 2016;5:9-26.
5. Persatuan Peneliti Hati Indonesia (PPHI), 2017. Konsensus nasional penatalaksanaan hepatitis B di Indonesia. PPHI. Jakarta: 2017
6. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. Nature reviews Gastroenterology & hepatology 2014; 11:209-19.
7. Ross DS. Graves' hyperthyroidism in nonpregnant adults: Overview of treatment [serial online]. Uptodate, 2019 [cited 20 October 2019]. Available from: https://www.uptodate.com/contents/graves-hyperthyroidism-in-nonpregnant-adults-overview-of-treatment.
8. Ross DS. Diagnosis of hyperthyroidism [serial online]. Uptodate, 2019 [cited 20 October 2019]. Available from: https://www.uptodate.com/contents/diagnosis-of-hyperthyroidism?search=graves%20ophthalmopathy&topicRef=7872&source=see_link.
9. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-421.
10. Aggarwal R, Chugh P. Thyrotoxic periodic paralysis: a short clinical review. Int J Res Med Sci 2015;3:539-42.
11. Sutjahjo A, Wironegoro R, Prajitno JH. Tirotoksikosis periodik paralisis. In: Tjokroprawiro A, Setiawan PB, Effendi

C, Santoso D, Soegiarto G, eds. Buku ajar ilmu penyakit dalam. Edisi-2. Surabaya: Airlangga University Press (AUP); 2015.p.147-51.

12. Kung AW. Thyrotoxic periodic paralysis: a diagnostic challenge. J Clin Endocrinol Metab 2006;91:2490-5.
13. Gutmann L, Conwit R. Thyrotoxic periodic paralysis [serial online]. Uptodate, 2018 [cited 20 October 2019]. Available from: https://www.uptodate.com/contents/thyrotoxic-periodic-paralysis?search=Thyrotoxic%20periodic%20paralysis&source=search_result&selectedTitle=1~13&usage_type=default&display_rank=1
14. Stan MN, Garrity JA, Bahn RS. The evaluation and treatment of graves ophthalmopathy. Medical Clinics 2012;96:311-28.
15. Davies TF, Burch HB. Treatment of Graves' orbitopathy (ophthalmopathy) [serial online]. Up to date, 2018 [cited 20 October 2019]. Available from: https://www.uptodate.com/contents/treatment-of-graves-orbitopathy-ophthalmopathy?search=Treatment%20of%20Graves%27%20orbitopathy%20(ophthalmopathy)&source=search_result&selectedTitle=1~57&usage_type=default&display_rank=1
16. López-Serrano P, de la Fuente Briongos E, Alonso EC, Pérez-Calle JL, Rodríguez CF. Hepatitis B and immunosuppressive therapies for chronic inflammatory diseases: When and how to apply prophylaxis, with a special focus on corticosteroid therapy. World J Hepatol 2015;7:539-47.
17. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance.Hepatology 2018;67:1560-99.
18. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215-9.
19. Kim HY, Kim W. Chemotherapy-related reactivation of hepatitis B infection: updates in 2013. World J Gastroenterol 2014;20:14581-8.