A Case of Thyrotoxic Periodic Paralysis and Moderate to Severe Grave’s Ophthalmopathy Requiring Intravenous Steroid Therapy with a Comorbidity of Chronic Hepatitis B Infection

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ABSTRACT
Grave’s disease is an autoimmune thyroid disease with several characteristic symptoms and signs. Grave’s ophthalmopathy, an inflammatory disease in the orbital area, is the primary extrathyroid manifestation of Grave’s disease. About 5% of Grave’s ophthalmopathy patients have moderate to severe severity requiring high doses of systemic corticosteroid therapy. Grave’s disease also has a 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 coincident with other diseases (e.g., Grave’s ophthalmopathy). The need for a high dose of corticosteroid therapy in treating Grave’s ophthalmopathy is a risk of reactivation in hepatitis B infected patients. This paper presented a Grave’s disease patient complicated with Grave’s ophthalmopathy who developed limb muscle weakness. The patient will receive high doses of corticosteroids and prophylactic lamivudine therapy to prevent hepatitis B virus reactivation.

Keywords: Grave’s Disease, Thyrotoxic Periodic Paralysis, Grave’s Ophthalmopathy, Hepatitis B Reactivation

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INTRODUCTION
Grave’s disease is an autoimmune disease characterized by the presence of autoantibodies of thyroid-stimulating hormone (TSH) receptors, causing hyperthyroidism. One of the complications that can occur in patients with Grave’s disease is thyrotoxic periodic paralysis (Sutjahjo et al., 2015). Thyrotoxic periodic paralysis (TPP) 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 Grave’s disease (Vijayakumar et al., 2014). About 20 to 25 percent of Grave’s disease patients have clinical features of Grave’s orbitopathy (ophthalmopathy) (Davies & Burch, 2019). Grave’s ophthalmopathy (GO) is an eye disorder that is the primary extrathyroid manifestation of Grave’s disease resulting from thyroid dysfunction. Intravenous high-dose corticosteroid is the initial treatment for moderate to severe active Grave’s ophthalmopathy disease (Bartalena et al., 2016).

Chronic hepatitis B (HBV) infection is a significant health problem affecting approximately 350 to 400 million people worldwide (PPHI, 2017). Patients with chronic HBV infection risk 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 (Hwang & Lok, 2014).

The key to preventing HBV reactivation is the identification of patients with HBV infection and providing prophylactic antiviral therapy in patients at high risk (Hwang & Lok, 2014). The following is a case report of a patient with Grave’s disease complicated with thyrotoxic periodic paralysis and Grave’s ophthalmopathy receiving high-dose corticosteroid therapy in the coincidence of chronic hepatitis B infection.

CASE REPORT
April 2018
A man, 32 years old, came to the emergency room of Dr. Soetomo General Hospital with a chief complaint of lower limb weakness.

Current medical history
The patient complained about having lower limb weakness that felt suddenly 4 hours before entering the emergency room. The patient had started complaining that the limbs were difficult to move before but could still walk. Similar symptoms happened in January and December 2017 but got better the next day without therapy. The patient also complained about having pain in the back of both eyes since three months ago, especially aggravated by moving the eyes.
Besides that, the patient complained of swollen eyelids, red eyes, and double vision. He was planning to receive 750 mg intravenous methylprednisolone injection once a week for six weeks. He denied shortness of breath, slurred speech, headache, vomiting, fainting, fever, and cough. There is increasing in appetite with a frequency of 4-5 times a day. There are no complaints of defecating and urinating.

Previous medical history
The patient was diagnosed with Grave’s disease in 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 an intravenous drug user, free sex, and transfusions was denied.

Socioeconomic history
The patient works as a construction worker. The patient has smoked since ± ten years ago.

Physical examination
From the physical examination, we found the general condition of weakness with GCS 4/6. His body weight was 65 kg and 165 cm in height. Blood pressure 130/80 mmHg, pulse 96 x / minute, regular rhythm, breaths 20 x / minute, and axillary temperature 36.7°C.

The head and neck examination revealed exophthalmos, Stellwag Sign, and Dalrymple’s Sign. There was no conjunctiva 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, and right-left intraocular pressure was 17.6, with proptosis, palpebral edema, and hyperemic conjunctiva. Funduscopy examination was 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.

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

We obtained a flat abdomen with normal bowel sounds from the abdominal examination. There was no collateral vein dilation, medusa head, organomegaly. There is no tenderness in all areas of the abdomen. The extremities examination showed that the acral limb is warm, dry, and red. There was a neurological motor deficit with a muscle strength value of 4 in all four extremities but no pathological reflex or sensory deficits. There are no enlarged lymph nodes in the armpits and groin. There were no petechiae, pustules, bullae, squama, and rash, with normal skin turgor.

Additional examination
From laboratory examination, we found Hb 15.0 g/dl, Hct 45.2%, leukocytes 9,170/mm³, platelets of 254,000 / mm³, 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 SGOT, 29 U / L SGPT, 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.

Assessment and management
Based on the history taking, physical and supporting examinations, the patient was diagnosed with Thyrotoxic Periodic Paralysis (TPP), 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. The patient is also planning for a fibroscan examination and serial ECG. The patient is given 2100 kcal/day with a low-carbohydrate, high-protein diet, KN2 infusion of 1000 ml for 24 hours, Thyrozol 10 mg every 24 hours, Propranolol 20 mg for every 8 hours, and KSR tablet every 12 hours.

Disease Course
On the 2nd day of treatment, the weakness of the lower limbs improved as the patient could walk around the bed. There is no palpatting, nausia, or vomiting. BP 130/70, regular HR 86x / minute, RR 18x / minute, and axillary temperature 36.8°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. Blood gas analysis results were Ph 7.42, PO2 82, PCO2 40, HCO3 22.5, BE 1.4, and SpO2 96%.

The patient was diagnosed with Thyrotoxic periodic paralysis, Hepatitis B, and Grave’s ophthalmopathy. An ophthalmologist, Endocrinologist, and Gastroenterologist consulted him. The ophthalmologist advised giving the patient 750 mg methylprednisolone weekly six times and continued with 500 mg weekly six times. The endocrinologist suggested a low carbohydrate, high protein diet and correction of potassium maximum of 50 meq/24 hours. Propranolol was planned to be discontinued if the EKG sinus rhythm. The gastroenterologist gave the patient 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°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, thyroxol 1x10 mg, education to reduce carbohydrates while eating, and routine control at gastroenterohepatology, endocrine, and eye clinic. One week later, the control at the patient’s gastro clinic performed a fibroscan examination with results according to F0-F1.

DISCUSSION
Grave’s 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
Thyrotoxic periodic paralysis (TPP) attacks are generally triggered by 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 the 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. Some other trigger factors are a high carbohydrate diet, high salt intake, trauma, strenuous exercise, exposure to cold, and alcohol consumption. Some drugs, such as diuretics, estrogens, and laxatives, can also trigger TPP (Aggarwal & Chugh, 2015; Kung, 2006; Vijayakumar et al., 2014). Typical ECG findings on TPP include sinus tachycardia, increased QRS voltage, PR interval abnormalities, and grade 1 AV block (Kung, 2006, Guttmann & Conwit, 2018).

Thyrotoxic periodic paralysis treatment has two main objectives: 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 ≤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 they can be given during acute attacks and prevent recurrent attacks. This drug is given at 20-80 mg every eight hours. TPP will resolve if the euthyroid condition is achieved, so definitive therapy of hyperthyroidism with radioiodine ablation or thyroidectomy is also a treatment option for TPP (Aggarwal & Chugh, 2015; Sutjahjo et al., 2015; Kung, 2006; Guttmann & Conwit, 2018; Vijayakumar et al., 2014).

This patient has a triad of TPP, which includes hypokalemia, muscle weakness, and thyrotoxicosis. He has a 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. This patient received an infusion of KCl ≤50 mEq per day and propranolol 20 mg every 8 hours orally on a low carbohydrate diet. Urine potassium values and blood gas analysis were within

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normal limits. ECG results show sinus tachycardia and abnormal PR interval.

Grave’s ophthalmopathy (GO) is an inflammatory eye disease that develops in orbit and is associated with autoimmune thyroid disorders. In most cases (± 90%), GO occurred in patients with current or past Grave’s disease. About one-third of patients with Grave’s hyperthyroidism have some signs and/or symptoms of GO, and only 5% have moderate to severe GO disease (Ross et al., 2016). Most patients with GO show mild signs and symptoms such as corneal irritation, periorbital 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, vision-threatening corneal ulcers, or optic neuropathy. Another study states that the incidence of optic nerve neuropathy threatening blindness is less than 2% (Stan et al., 2012).

Several risk factors such as genetics, smoking, thyroid dysfunction, radioactive iodine, and TRAb can affect the development or progression of GO. Smoking is the strongest and most consistent risk factor for GO progression and has a worse response to therapy (Davies & Burch, 2019; Stan et al., 2012). 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 increased risk. 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 (Davies & Burch, 2019; Stan et al., 2012).

Proper management of GO is based on the 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 threatening vision 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, which tends to respond to corticosteroid therapy (Stan et al., 2012; Davies & Burch, 2019).

Patients with GO are treated according to the severity of the disease. Treatment of GO patients includes management of hyperthyroidism (if any), smoking cessation, and local therapy to reduce eye irritation and 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, and thyroidectomy therapy. Some authors suggest six months of selenium therapy for patients with mild ophthalmopathy. Selenium can improve soft tissue swelling in certain patients. Radioiodine is a contraindication for moderate/severe to vision-threatening ophthalmopathy as it worsens the condition. Severe ophthalmopathy is characterized by deteriorating diplopia, exposure keratitis, and/or optic neuropathy causing visual disturbances. Severe ophthalmopathy requires steroids, orbital decompression, or radiotherapy (Davies & Burch, 2018; Sutjahjo et al., 2015). 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 six weeks, followed by 0.25 g once a week for six 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 six weeks, followed by 0.5 g once a week for six weeks (cumulative dose of 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 (Bartalena et al., 2016).

Grave’s disease was complicated by GO with severe, excessive proptosis symptoms in this patient. 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 an active disease with a moderate/severe degree. The patient received high-dose methylprednisolone at an initial dose of 0.75 g once a week for six weeks, followed by 0.5 g once a week for six 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 risk reactivation using immunosuppressive therapies such as chemotherapy, immunosuppressants, anti-CD20 antibodies, TNF inhibitors, or corticosteroids. (López-
Hepatitis B virus reactivation is the re-emergence of the active necro-inflammatory disease. This condition is characterized by a 1.5-2-fold increase in ALT and viral load DNA of more than 2000 IU/mL in inactive hepatitis B carriers or in patients who become HBV DNA positive after being previously diagnosed as having resolved hepatitis B infection (López-Serrano et al., 2015). 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. Close monitoring is needed for low-risk patients, and antiviral therapy can be started immediately if the first sign of HBV reactivation is detected (Hwang & Lok, 2014).

The American Association for the Study of Liver Diseases (AASLD) and European Association for the Liver Diseases (EASL) have developed guidelines for the management of HBV reactivation (López-Serrano et al., 2015). These guidelines recommend the use of prophylactic antiviral therapy in patients at moderate to high risk for HBV reactivation, with close monitoring of low-risk patients. Immediate antiviral therapy should be initiated if the first sign of HBV reactivation is detected.

### Table 2. Clinical activity score (Davies & Burch, 2019)

| 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 |
| Chemosis (edema of the conjunctiva) | X | | 1 |
| Swollen caruncle (fleshy body at medial angle of eye) | X | | 1 |
| Increase in proptosis ≥ 2 mm | X | | 1 |
| Decreased eye movements ≥ 5° in 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.

### Table 3. Risk stratification of Hepatitis B reactivation (Hwang & Lok, 2014; Reddy et al, 2015)

| Risk level | Positive HBsAg | Negative HBsAg and Positive Anti-HBc | Antiviral therapy |
|------------|----------------|-------------------------------------|------------------|
| High risk  | Chemotherapy   |                                     | Prophylactic therapy |
|            | Anthracycline class (daunorubicin, epirubicin) | | |
|            | B-cell-depleting agents, such as anti-CD20 (rituximab, obinutuzumab) | | |
|            | Immunosuppressive therapy for transplantation | | |
|            | Steroid therapy combined with other immunosuppressive therapy | | |
|            | Moderate or High-dose steroid therapy for more than 4 weeks. Moderate dose equivalent to 10-20 mg prednisone and high dose equivalent of >20 mg prednisone | | |
| Moderate risk | Chemotherapy for solid tumour | | Consider prophylactic therapy or pre-emptive therapy |
|            | Anthracycline class | | |
|            | Cytokine inhibitor or other integrin inhibitor (rhenium, nasturtinum, vedolizumab) | | |
|            | Tyrosine kinase inhibitor (imatinib, sunitinib) | | |
|            | Other immunosuppressive therapy without steroids | | |
|            | (azathioprine, 6-mercaptopurine, methotrexate) | | |
|            | Low dose steroid (<10 mg prednisone) for more than 4 weeks | | |
| Low risk   | Any dose of steroid therapy less than 1 week | | No need for prophylactic therapy, pre-emptive therapy only if there's sign of reactivation |
|            | TNF-α inhibitor | | |
|            | Other immunosuppressive therapy without steroids | | |
|            | Low dose steroid for more than 4 weeks | | |
|            | Any dose of steroid therapy less than 1 week | | |
Study of the Liver (EASL) guidelines recommend preemptive 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 are defined as immunosuppressive therapy, so prophylactic treatment should be considered. A low steroid dose given less than two weeks does not require prophylaxis. Prophylactic treatment is given 1 to 3 weeks before immunosuppressive therapy starts and continued for six 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 (López-Serrano et al., 2015; Terrault et al., 2018).

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 a sign of reactivation (Table 3) (Hwang & Lok, 2014; Reddy et al., 2015).

The evidence regarding choosing a suitable 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 a higher genetic barrier to resistance. Entecavir and tenofovir are relatively safe options and have great potential with low resistance for long-term immunosuppressant treatment (Kim & Kim, 2014; López-Serrano et al., 2015).

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

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

CONFLICT OF INTEREST
The authors declare there is no conflict of interest.

AUTHOR CONTRIBUTION
All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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