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Case Report

Polymyositis concomitant with hepatitis B virus infection: Treatment challenges

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Abstract

Polymyositis is a chronic autoimmune disease that presents with symmetrical progressive proximal muscle weakness. The cause of this disease due to abnormal activation of macrophages that might be associated with systemic diseases such as other autoimmune diseases, malignancy or viral infections including hepatitis B virus. The aim of this case report was to highlight treatment challenges in a patient with polymyositis concomitant with hepatitis B. A 28-years-old man with history of completed hepatitis B treatment with negative viral load presented with symmetrical progressive weakness on both inferior proximal extremities. The patient complained of pain predominantly in both tights and calves. No dermatological manifestation was observed. Elevated muscle enzymes and liver function were observed. Along with the course of the disease, hepatitis B reactivation was discovered as hepatitis B virus DNA was re-detected. Treatment options of this patient (polymyositis concomitant with hepatitis B viral infection) remain challenging. The main treatment of polymyositis consists of high dose methylprednisolone and this immunosuppressant could worsen the hepatitis B virus infection. The patient was finally treated with combination of mycophenolic acid and methylprednisolone for polymyositis and entecavir for hepatitis B. After one month of treatment, the patient showed a clinical improvement. This case highlights that viral screening must be done prior to starting polymyositis treatment as it could concomitant with viral infections such as hepatitis B. Antiviral prophylaxis must be given 1–2 weeks before immunosuppression starts. Management for both polymyositis and hepatitis B is important with entecavir or tenofovir as the optimal agents against hepatitis B virus.

Keywords: Polymyositis, idiopathic inflammatory myopathy, hepatitis B, autoimmune, rheumatology

Introduction

Polymyositis is a chronic autoimmune disease that presents with symmetrical progressive proximal muscle weakness and it is one of the four major subtypes of idiopathic inflammatory myopathies (IIM) [1]. The incidence of idiopathic inflammatory myopathies varied, with estimation ranging from 0.2 to 2 per 100,000 person-years while prevalence ranged from 2 to 25 per 100,000 people [2]. Polymyositis as one of the four major subtypes of (IIM) has estimated prevalence of 5 to 22 per 100,000 persons and the incidence is estimated around 1.2 to 19 per million persons per year. The incidence rate of polymyositis is double in women than men with estimation ranged from 2–3:1. Peak incidence often found in group age between 50 to 60. The incidence of polymyositis has been increasing recently since there are increase in detection rate [3]. Abnormal activation of cytotoxic T lymphocytes (CD8 cells) and macrophages against

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muscular antigens lead to inflammatory muscle degeneration play a main role in developing this disease [4,5]. The cause of this abnormal activation of CD8 cells and macrophages might be associated with systemic diseases such as other autoimmune diseases, malignancy or viral infections including hepatitis viruses [1]. A study showed that inflamed muscle of polymyositis patients was dominated with CD4 and CD8 T cell infiltration [6]. CD4 and CD8 T cell can be found in the early until late phase of this disease [6]. Other related cytokines such as IL-1 alpha and IL 17 also associated with direct damage to muscle cells via nuclear factor kappa B (NF-κB) [7]. NF-κB can increase the expression of major histocompatibility (MHC-1) class and disrupt the differentiation process of myocytes. The release of inflammatory mediators especially IL-21 in muscle and serum of affected patient can also lead to indirect damage to muscle fibers [7].

Main treatment for this disease is immunosuppressive agents such as glucocorticoid, intravenous immune globulin, conventional disease-modifying antirheumatic drugs (DMARD) and biologic DMARD [8]. One of the well-recognized side effects of immunosuppressive treatment is hepatitis B virus (HBV) reactivation. HBV reactivation is defined as an increase in serum HBV DNA compared to the normal level or the detection of HBV DNA in a previous undetected HBV DNA or conversion of HBsAg from negative to positive [9]. A study reported high HBV reactivation in patients with rheumatic diseases who were receiving biological and non-biological DMARD although the prevalence is slightly higher in patients receiving biological DMARD than non-biological DMARD [10]. Half of patients who received non-biological DMARD had HBV reactivation after receiving pulse dose steroid therapy [10]. A case report described a case of 81-years old woman with dermatomyositis and chronic HBV infection treated with high dose of steroid and methotrexate without antiviral prophylaxis [11]. Four months later, the patient readmitted with HBV reactivation and was treated with tenofovir but the patient was expired due to liver failure [11]. In this case report, a case of polymyositis concomitant with hepatitis B was described. The aim of this case report was to provide diagnostic and therapeutic approaches and to highlight the challenges. This report emphasizes the importance of screening for hepatitis B before administering immunosuppressive agents.

Case

A 28-years-old man referred to rheumatology outpatient clinic from neurology outpatient clinic at H. Adam Malik General Hospital, Medan, Indonesia with complaint of knee pain and suspect of osteoarthritis on February 2023. The patient also presented with weakness on both of the tights in the past two years. The weakness was progressive and getting more severe. Due to the weakness, patient could not walk or stand for too long. Patient was difficult in getting up from a sitting position. Patient also reported sore in both of the calves. Stiffness and pain in both of knee were also found especially in the morning. Other presentations such as weakness in both hands or neck and pain in other joints were denied by the patient. Skin manifestations were also not found. History of trauma was denied by the patient. History of autoimmune disease in family was not found. Past medical history was hepatitis B.

In 2018, the patient was diagnosed with hepatitis B. Patient had no specific symptoms such as fever, malaise, jaundice or right upper quadrant pain. The diagnosis was made during a medical check-up to apply for a job. Risk factors for hepatitis B such as birth from an infected person, multi-partner sex, abuse of alcohol, blood transfusion, sharing contaminated needles, or items were denied by the patient. Patient was treated with telbivudine since 2018 and in 2020, the patient had stopped the medication since the HBV DNA was undetected thrice.

In early 2021, the patient complained a sudden weakness in both of proximal inferior extremity. Fever prior to the weakness was denied by the patient. At first, patient thought the complaint of weakness was due to activities. Patient had traditional massaged every day for almost one month, but there was no improvement and the weakness became worse. Patient then decided to continue the treatment to neurology outpatient clinic of H. Adam Malik General Hospital and was diagnosed with myositis. Patient received methylprednisolone 4 mg twice a day for two months. The patient claimed to have slight improvement even though the weakness still persists. The medication was stopped and patient was referred to medical rehabilitation for physiotherapy twice a week for a year, but still there was no significant improvement. Patient

went back to neurology outpatient clinic and was referred to rheumatology outpatient clinic with the suspicion of knee osteoarthritis (February 2023).

From physical examinations, vital signs were within normal limits. There was no crepitation, redness or warmth in both of the knee. The motoric strength of upper extremity was normal (55555/55555) and lower extremity was found to be decreased (33555/33555). Examinations of other organ systems were normal. Laboratory examinations showed platelet count, erythrocyte sedimentation rate, c-reactive protein, antinuclear antibody (ANA), ANA immunofluorescence, anti dsDNA, ANA profile, urinalysis and renal function test were within normal limits. Hemoglobin was slightly increased 17 g/dL, leukocyte also increased 19.750/mm3, HBV surface antigen (HBsAg) and HBV e antigen (HBeAg) was reactive. The HBV DNA was detected at 55,441,342 IU/mL and obtained before mycophenolic acid was administered. Both of the liver function enzymes were increased, aspartate transaminase (AST) was 203 U/L and alanine transaminase (ALT) was 542 U/L. Muscle enzymes were also increased, creatinine kinase (CK-NAC) was 6.724 U/L and lactate dehydrogenase (LDH) was 798 U/L.

The patient had electromyography (EMG) from neurology outpatient clinic and the results showed a diffuse myogenic lesion which described myositis (**Figure 1**). Magnetic resonance imaging (MRI) was conducted twice. The first MRI which was whole spine MRI conducted during the treatment from neurology outpatient clinic with the results showed no deformity or intensity change in vertebra and spinal cord. The second MRI was a right tight MRI which conducted during treatment from rheumatology outpatient clinic. The result showed a characteristic of myositis with an intensity change and atrophy of vastus medialis, intermediate, lateralis and biceps femoris muscle (**Figure 2**). During the treatment in rheumatology department, the patient underwent ultrasonography for suspicion of knee osteoarthritis and it was within normal limits. Muscle biopsy of left gastrocnemius was also conducted and the result showed nonspecific chronic inflammatory process suggesting polymyositis (**Figure 3**).

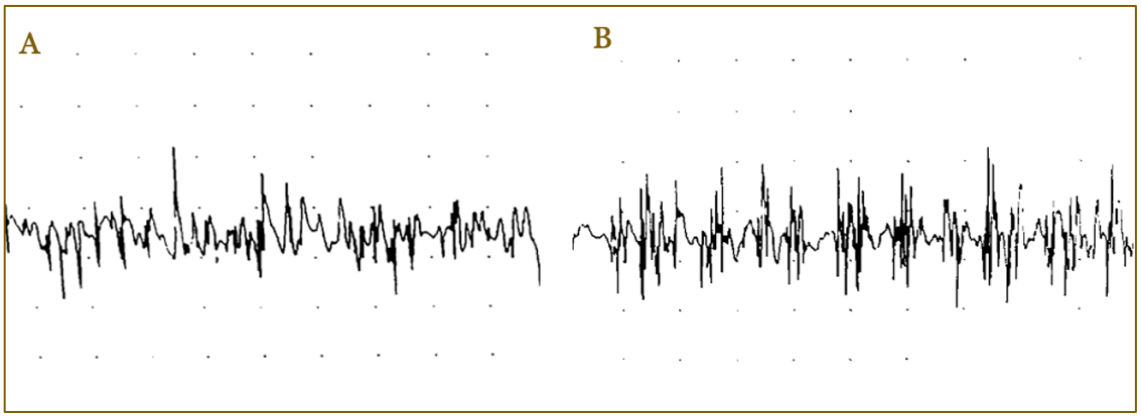

Figure 1. Electromyography (EMG) of left rectus femoris (A) and left anterior tibialis (B) showed myogenic lesion with short, small, low amplitude polyphasic motor unit potentials fibrillation potentials even at rest; and bizarre, high frequency repetitive discharges. EMG is 500 µV/Div with 20 ms/Div.

Based on the clinical features, evaluation of laboratory and radiology examination, the patient was diagnosed with polymyositis. The patient was treated with methylprednisolone 24 mg tapering off. A week later, patient complained sore through all the body. The dose of methylprednisolone was then lowered gradually to 4 mg once a day. Methylprednisolone was still continued although it had been tapered off to once daily as methylprednisolone was the main therapy for polymyositis. The patient was then planned to receive mycophenolic acid 360 mg twice a day. Mycophenolic acid administration was delayed as HBsAg was reactive. The administration of mycophenolic acid as immunosuppressant could worsen the HBV infection if the infection was not treated first. Mycophenolic acid treatment can only be initiated when nucleotide agent had been given. Mycophenolic acid was finally administered in late July 2023, 4 months after the high dose methylprednisolone initiated. The patient also received entecavir 0.5 mg once a day from gastroenterohepatology outpatient clinic for the management of hepatitis B reactivation. Entecavir was administered a week before Mycophenolic acid was given.

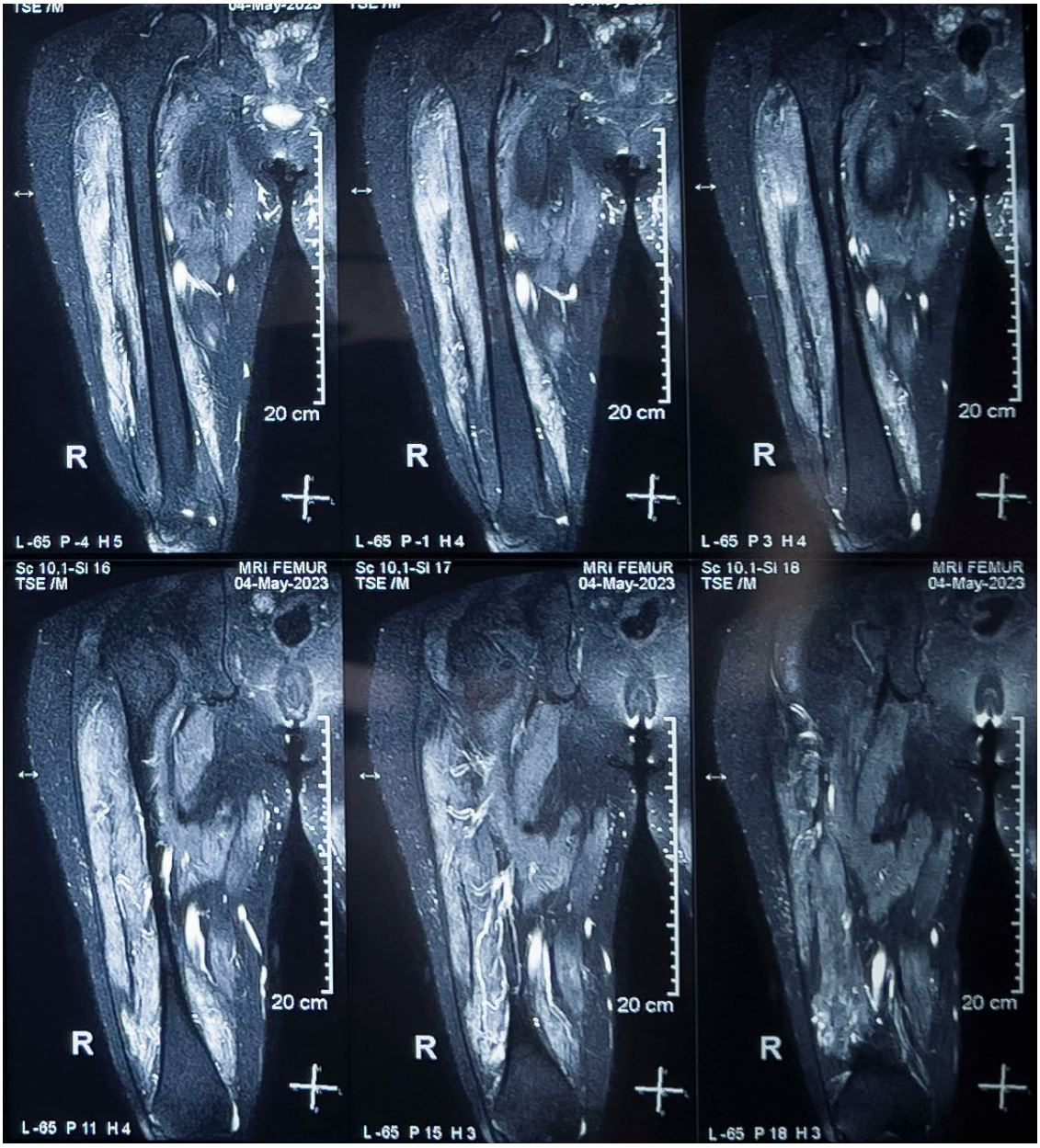

Figure 2. Magnetic resonance imaging (MRI) findings on right femur muscle show intensity changes with atrophy of the vastus medialis, intermediate, lateralis and biceps femoris muscles that indicates myositis.

After five months of treatment with methylprednisolone and two weeks of mycophenolic acid, evaluation of muscle enzyme was conducted. Blood test revealed slight decrease in AST (202 U/L), ALT (338 U/L), LDH (689 U/L) and increase in CK-NAC (7,646 U/L). Although muscle enzyme was still increased, patient told there was slight improvement in which patient could now stand up for a longer period and climb up 3-storey-house without significant limitation. Treatment from rheumatology and gastroenterohepatology outpatient clinic remained continue. A month later, routine evaluation of muscle enzyme was conducted and revealed decrease in all parameters such as AST (145 U/L), ALT (215 U/L), LDH (529 U/L) and CK-NAC (5,964 U/L). Symptoms of weakness had been improved significantly compared to the first-time patient admitted to rheumatology outpatient clinic. Motoric strength of upper extremities remained normal (55555/55555) and lower extremities had been increased (44555/44555). Pain and stiffness especially in the morning had also been improved. The only symptom that still persist was the patient's inability to get up from a sitting position without the help of hand support. Evaluation of HBV DNA will be conducted.

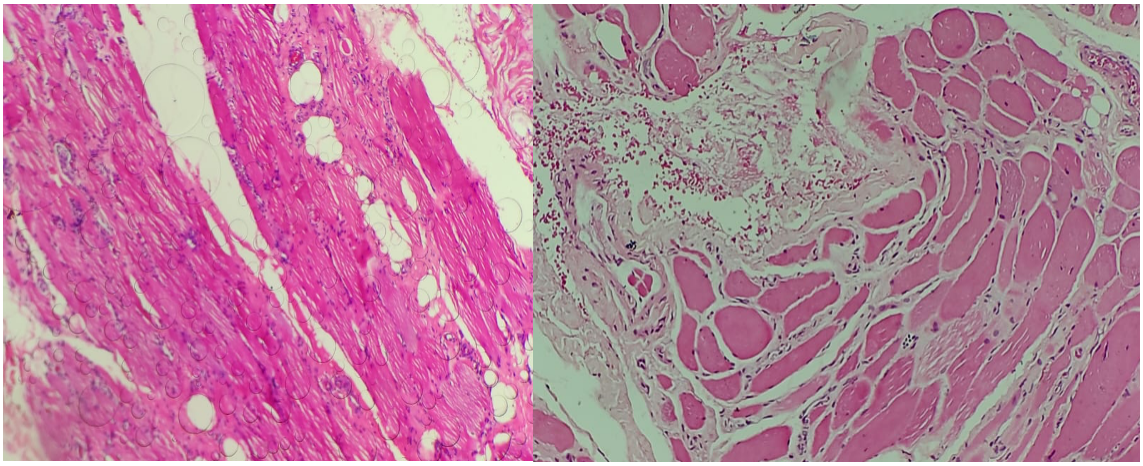

Figure 3. Histopathology of gastrocnemius sinistra muscle show nonspecific chronic inflammatory process.

Discussion

Polymyositis is one of the four major subtypes of idiopathic inflammatory myopathies. The three other idiopathic inflammatory myopathies are dermatomyositis (DM), sporadic inclusion body myositis (sIBM) and necrotizing autoimmune myopathy (NAM) [8]. Polymyositis is a very uncommon disease that primarily affects adults rather than children and affects more women than men [12]. The incidence of this disease increases after second decade of life with peak incidence occurs between the ages of 45 and 60 [13]. The incidence of polymyositis varied according to regions. A study in Australia revealed the incidence of polymyositis 4.1 per 1.000.000 people [13]. Another study conducted reported the incidence of polymyositis 0.75 per 100.000 person-years [14].

All subtypes of idiopathic inflammatory myopathies have hallmark symptom which is symmetrical progressive proximal muscle weakness [3]. It can affect either superior or inferior proximal muscle and neck flexor muscle also sometimes can be involved. Most commonly involved muscles are deltoid, hip flexor, abductor and extensor [8]. Patient typically complaint about difficulty in getting up from a sitting position and climbing up stairs. When superior proximal muscle involved, patient may complain difficulty in performing activities such as combing, brushing hair or any activities related to overhead abduction. Polymyositis can also progress to distal muscle but it rarely interferes with activities and usually milder [15]. In our case, the patient complained weakness in both of the proximal inferior muscle which was characterized by difficulty in standing for a certain period of time and getting up from a sitting position and climbing stairs. The patient also complained myalgia in both of distal inferior muscle, but it was mild and unobtrusive. Muscle atrophy was not found in the patient.

Physical examination must include motoric and sensory examination of affected muscles. Motor examination usually reveals a decrease in muscle strength while sensory examination within normal limit. The decrease of muscle strength can later be confirmed by electromyography examination. Joint pain and swelling can also be found and often misinterpreted as the cause of muscle weakness, as seen in this patient. Myalgia can be found in around 25 to 50% cases [1,15]. In this case, inferior muscle motor examination revealed a decrease of muscle strength and EMG examination indicated a diffuse myogenic lesion which described myositis.

Typically, complaints are accompanied by evidence of an increase in muscle enzymes such as creatine kinase, LDH, aldolase and transaminase. However, it must be noted that not all myopathy symptoms are always accompanied by elevation in those muscle enzymes [15]. In our case, patient showed an increase in creatine kinase, LDH and transaminase. Aldolase was not tested because the test was not available in our hospital.

Diagnosis of polymyositis can be made based on Bohan and Peter criteria [16]. Definite diagnosis of polymyositis can be made when all four criteria are met: (a) progressive proximal muscle weakness with or without dysphagia; (b) muscle biopsy with evidence of myositis; (c) elevation of muscle enzymes such as CK, LDH, transaminase and aldolase; and (d) EMG triad for

myopathy (short, small, low-amplitude polyphasic motor unit potentials; fibrillation potentials even at rest; and bizarre, high frequency repetitive discharge) [16]. In this case, the patient met all four criteria from Bohan and Peter criteria which can be interpreted as definite polymyositis. Based on classification criteria by European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2017 [17], the patient had a score of 9.4 with 95% probability indicating a definite idiopathic inflammatory myopathy with polymyositis as the subgroup.

The main goal of polymyositis treatment is to improve muscle strength and prevent extra muscular complications. The first line treatment of polymyositis mainly includes high dose of corticosteroid. Prednisone and methylprednisolone are among the most prescribed corticosteroid with initial dose of 1 mg/kg up to maximum dose of 80 mg/day [18]. After initial dose, it should be tapered down each week as high dose of corticosteroid more than six weeks increase the risk of corticosteroid-induced myopathy [18,19]. Evaluation shall be done every few weeks. Muscle enzymes usually will decrease progressively within several weeks until reaching normal in the six weeks [20]. In this case, treatment became challenging due to hepatitis B. The association between polymyositis and hepatitis B remain unclear, but the presence of antibody complexes against the hepatitis B antigen in muscle raises the possibility that link hepatitis B with polymyositis as triggering antigen [21]. It is also supported with the increase of myositis-associated antibodies found in patient with HBV infection more than patient without HBV infection [22]. Main treatment of polymyositis such as corticosteroid can cause suppression of T-cell cytotoxic which may lead to decrease immune ability against the virus and increase HBV-DNA replication through activation of corticosteroid-responsive transcriptional regulatory element which has been detected in HBV genome [9]. The risk of HBV reactivation will also increase when administered in medium to high doses (>20 mg/day) for more than three months [9]. A study classified corticosteroid as high risk when administered >10 mg/day for more than four weeks, medium risk when <10 mg/day for more than four weeks and low risk when <10 mg for less than a week [23]. An observational study from Japan showed the incidence of hepatitis B reactivation in resolved HBV infected patients with rheumatoid arthritis was 1.35/100 person-years while other rheumatic diseases (systemic lupus erythematosus, vasculitis syndrome, myositis and polymyalgia rheumatica) was 3.61/100 person-years corticosteroid [24]. Most of the patients in rheumatoid arthritis group were treated with methotrexate while other rheumatic diseases group received an average dose of 9.03 mg corticosteroid [24].

Second line treatment for polymyositis include steroid-sparing immunosuppressive agents such as azathioprine and methotrexate [18]. In terms of treatment concomitant with hepatitis B reactivation, azathioprine can be considered safe as incidence of HBV reactivation are extremely rare [25]. However, the use of azathioprine or methotrexate can worsen the liver function in patient with polymyositis as these drugs are hepatotoxic [26]. Mycophenolate mofetil, an inosine monophosphate dehydrogenase inhibitor, is an alternative for second line treatment for polymyositis when no response to methotrexate or azathioprine [18]. In this case patient was treated with mycophenolic acid 360 mg twice a day as it is the safest choice among the other conventional DMARD and may have beneficial effect towards hepatitis B infection. An in vitro study showed that mycophenolate mofetil had an inhibition effect on HBV replication [27]. It is supported by another study which reported mycophenolate mofetil combination with lower dose prednisone (0.5 mg/kg) recorded a lower reactivation of hepatitis B compared to monotherapy of prednisone (1 mg/kg) [28]. These data suggest that corticosteroid could induce HBV reactivation [28].

Management of HBV reactivation may differ in each patient. Patient's HBV status such as chronic or resolved infection and the use of immunosuppressive agents should be taken into consideration while choosing antiviral agents [29]. Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI) used to know as treatment choice for HBV reactivation, but it has high risk of drug resistance [30]. Newer nucleoside analogues such as entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide have lower risk of drug resistance with high potent against hepatitis B [29]. It is now become the first choice in the management of hepatitis B [9].

A case of polymyositis and HBV reactivation was reported previously of which a 57 years old woman with polymyositis clinical presentation and HBV reactivation [31]. The patient received monotherapy of entecavir 0.5 mg for 10 weeks followed by combination with 30 mg

methylprednisolone tapering off. The treatment resulted in gradual decrease of liver enzymes, improved muscle weakness and decreased creatine kinase level. This suggests the importance of oral corticosteroids as main treatment in improving the symptoms of polymyositis due to its immune related. However, when active hepatitis B present, the infection should be priority to be resolved.

Antiviral prophylaxis should always be considered in moderate and high risk of HBV reactivation. Prophylaxis should be given 1–2 weeks before starting immunosuppressive agent. Guideline from European Association for the Study of the Liver (EASL) recommends entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide as prophylaxis agents and should be continued for at least 12 months after the immunosuppressive agent was stopped [32]. Prophylaxis can be stopped when the underlying disease is under remission [32].

Patient with chronic active HBV infection should always be consulted to gastroenterohepatology unit and treated with either entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide. For patient that has never been infected with HBV, vaccination of hepatitis B should be considered and ideally given before the start of immunosuppression. EASL has recommended antiviral therapy for all patients with detected HBV DNA [32]. In this case, patient had a reactivation of hepatitis B and was consulted to gastroenterohepatology unit. The patient received entecavir 0.5 mg once a day and the HBV DNA will be evaluated.

As a limitation of this case, nucleotide agent was not given immediately when HbsAg was reactive. Entecavir, one of the nucleotide agents was given after the patient received a low dose of corticosteroid for around four months. Ideally, nucleotide agent should be given one week prior to immunosuppression therapy with or without detectable HBV DNA.

Conclusion

Viral screening must be done prior to starting treatment for patients with polymyositis as it can concomitant with viral infection such as hepatitis B. Management for both polymyositis and hepatitis B is important with entecavir or tenofovir as the optimal agents against HBV.

Ethics approval

The informed consent has been obtained from the patient.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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