Case Report

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A Case of Polymyositis Associated with Cytomegalovirus Infection in a Patient with Hashimoto's Thyroiditis

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Abstract: Polymyositis is a rare condition with an unknown etiology occurring more frequently in adult women. There is a lack of evidence on the coexistence of PM and CMV infection in a patient with Hashimoto Thyroiditis hypothyroidism. However, the increasing incidence of CMV infection and autoimmune diseases overlapping points out a relationship, while the association direction re-mains unclear. Case outline: A 32-year-old woman recently treated for HT hypothyroidism was admitted to the hospital two weeks after being treated for common flu by the family doctor, com-plaining about a worsening condition with muscle pain, weakness, frequent falls, and fatigue. The first tests showed a normalized thyroid function, with elevated values of troponin and serum creat-inine kinase (KC). The immunological tests revealed the presence of a high titer of CMV IgG anti-bodies and raised levels of CMV DNA. Pelvis MRI images demonstrated markedly elevated signals on the STIR sequences in the pelvis, thighs, and calves, indicating active and severe multifocal my-ositis. The diagnosis of PM was confirmed with the muscle biopsy on day 7 of hospitalization. The patient showed significant improvements within two weeks after the medical therapy and physio-therapy.

Keywords: Polymyositis; Cytomegalovirus infection; Hashimoto`s thyroiditis; association; coexistence; autoimmune diseases

1. Introduction

Polymyositis (PM) is a subset of idiopathic inflammatory myopathies (IIMs), mani-fested by progressive muscle weakness, electromyography (EMG) alterations indicative of myopathy, biopsy evidence of inflammatory infiltrates, and changes in muscle enzymelevels [1,2]. It is a remarkably uncommon entity, affecting more women than men and rarely found in children [3]. Autoimmunity is a normal aftermath, which when aberratedcan result in loss of self-tolerance leading to autoimmune diseases. It covers a wide range of diseases from systemic diseases including lupus erythematous and PM to organ-spe- cific diseases like Hashimoto Thyroiditis (HT). These diseases are characterized by the generation of a large range of autoantibodies targeting multiple autoantigens. Despite the fact that the etiology of these diseases is not completely understood, environmental, genetic, and immunological factors contribute to the phenomenon of their etiology, referred to as the "mosaic of autoimmunity"[4]. Although it is generally acknowledged that there is an association between autoimmune thyroid disorders and systemic autoimmune dis- eases [3–7], there are very few reports available confirming a possible relationship be- tween PM and HT [8,9,10]. While the etiology of autoimmune diseases is not completely clear, PM is thought to be triggered by viruses such as coxsackie viruses, enteroviruses, retroviruses, parvoviruses, human T-lymphotropic virus (HTLV), and human immuno- deficiency virus (HIV) [11]. Cytomegalovirus (CMV), part of the herpesvirus family is ac- quired in the first years of life and is carried by 40-70% of the world's population[12]. Some evidence has shown that herpesviruses such as Ebstein Bar virus are linked to several

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autoimmune diseases including PM and HT [13]. However, there is a lack of evidence to support the hypothesis on the association between PM and CMV infection. We describe a 32-year-old woman newly diagnosed with HT hypothyroidism, presented with PM occurring simultaneously with CMV infection

2. Case Presentation

A 32-year-old woman diagnosed and treated for HT with hypothyroidism for less than one year was presented to the family doctor complaining about progressive muscle pain, fatigue, and a two-week history of daily sub-febrile temperature of.37,5° Celsius. The patient worked as an engineer and reported to be a nonsmoker, with no previous personal or family history of thyroid disorders, or autoimmune diseases, and without known allergies. The family physician diagnosed her with common flu, and she was given only paracetamol and vitaminic therapy for ten days. During the following days, the situation aggravated with progressive bilateral lower extremity weakness, walking difficulties, recur-rent falls, fatigue, and disability to perform daily activities. After 2 weeks she was admit-ted to the rheumatology department for further examinations. The first tests showed a normalized thyroid function with free thyroxine (free T4) level 19.2 pg/ml (normal range 12.0-22.0 pg/ml), thyroid-stimulating hormone (TSH) 1.87 μlU/ml (normal range 0.3-4.5 μlU/ml) with elevated troponin 4,95 ng/ml (normal range 0.0-3.37ng/L) and serum creatinine kinase (CK) levels 1038 U/I (normal range <195 U/I), ERS 5 mm/h. Blood test, red blood cell (RBC) $3.9x10^6$,(normal range 4-5x 10^6), white blood cell(WBC) $3.4x10^3$ (normal range 4.00-11.00 x 10^3), hemoglobin (HGB) 10.8g/dl (normal range 12.0-14.0), HCT 33.2 % (normal range 35.0- 50.0 %), platelets(PLT) $116x10^3$ (normal range 150-400 $x10^3$), erythro-cyte sedimentation 45 mm/h.

The immunological tests revealed the following results: IgA 1.38, IgG 7.1, IgM 76, C3 complement 12.7(90-180 mg/dl), C4 complement 22(10-40 mg/dl), and normal Rheumatoid Factor (RF) levels: <10 IU/mL (<15 IU/ml), Anti CCP <7 (normal range <17 U/mL). In addition, Extractable Nuclear Antigen (ENA) screening resulted in positive, Ro (SS-A) antibody positive, Anti-SRP-54 weak positive, Sm antibody positive, Proteinase 3 (PR3) antibody <0.2 (normal range 0-1 AI), and Myeloperoxidase (MPO) antibodies <0.2 (normal range 0-1 AI). While La antibody, RNP antibody, Jo-1 antibody, Scl-70 antibody, Ribosomal antibodies, myocardial antibody, and cardiolipin antibody were all negative. Results from other laboratory tests were as follows: TB gamma interferon negative, HBsAg negative, anti-HBc negative, HCV IgG negative, HIV 1, and HIV 2 antibody negative, and My-coplasma pneumonia antibody negative. Laboratory tests for Toxoplasma Gondi and EBV showed signs of infection at some time but no evidence of recent infection. CMV IgG was detected and CMV DNA was found to be 209512 IU/mL (normal range <200 copies/mL). Due to the high levels of CMV DNA, in consultation with the virology team, it was decided to start the treatment with valganciclovir.

EMG finding was abnormal and revealed the presence of fibrillation potential and positive sharp waves suggestive of myopathy. We then performed a cardiac MRI which showed: nondilated LV with normal systolic function, no LVH, normal RV Size, and systolic function, patchy non-ischemic fibrosis in the basal to mid inferior segment (border-line elevated native T1 values, normal T2 readings), and small bi basal pleural effusion, right > left. There was no evidence that the myocardium had been involved, which is consistent with the clinical picture of inflammatory myositis. Troponin T was elevated but presented more skeletal muscle release than cardiac involvement. To look for changes in the organs within the pelvis we performed a pelvic ultrasound transabdominal study which showed a retroverted uterus, appearing in normal shape and size (4.8x8x5 cm) with no obvious adnexal masses, cysts, or free fluid.

Images from pelvis MRI demonstrated an extensively increased signal on the STIR sequences within the visualized pelvis, thighs, and calves within multiple muscle groups consistent with active and severe multifocal myositis. A cardiac echo demonstrated a nor-mal-sized left ventricular cavity, normal LV systolic function by ejection fraction, no valvular dysfunction, and no pericardial effusion. Additionally, a PET scan was organized but it was refused by the patient.

A biopsy of the right biceps muscle was performed on day 7 of admission to the hospital and demonstrated mild and non–specific changes with noticeable myocyte phagocytosis. The structural

proteins investigated were normal. The features raised the possibility of a limb girdle dystrophy, but immune-mediated necrotizing myopathy (IMNM) was excluded as this is usually responsive to treatment. In this condition, muscle weak-ness is often severe with CK levels greater than 3000IU/L but there is no associated inflammation and increased expression of MHC Class I proteins, as in this case, is often absent. There is also often a poor response to steroid management, but other immunosup-pressive drugs may be efficient. The diagnosis was confirmed by the detection of the presence of anti- SRP autoantibodies.

According to the clinical traits, the laboratory findings, and based on Bohan and Peter criteria (14) the woman was diagnosed with PM and CMV infection concomitantly.

We, therefore, started the treatment with an IV methylprednisolone course, Pregiven 20 grams for 5 days, MTX 15 mg s/c weekly, Folic acid once weekly, Multivitamin 1 tab daily, 60 mg prednisone weaned down now to 30 mg, Bisoprolol 5 mg daily, Valganciclovir 900 mg twice daily, Lansoprazole 30 mg daily, Levothyroxine 100 mg, Fortisip 1 mg twice daily, Ivabradine 5 mg twice daily and Rituximab first doze followed by the second dose two weeks later.

Supplementing to medical the therapy, the patient followed physiotherapy sessions three times per week. These exercises have focused on her proximal and core control with bed, chair and standing exercises at a handrail. After the start of the treatment along with physiotherapy, there were improvements in her clinical features, in the number of steps she could complete and her trunk control despite being hampered by her fatigue. The laboratory tests showed that troponin and CK levels gradually dropped. After the second dose of Rituximab, the patient showed independent mobilization at a slow pace, and was able to sit and stand from chair and bed. The future treatment plan is as follows: Rituximab in the next 6 months, Methotrexate needs to be continued for 2-3 years mini-mum with regularly monitoring (blood test once every 1-2 months for FBC and LFTs) and Prednisolone will continue at 30 mg for 2 weeks it will be reduced with 5mg every two weeks to result at 10 mg dose after twelve weeks. Prednisolone 10 mg was then recommended to be followed for six months.

3. Discussion

Our patient was a 32-year-old woman diagnosed and treated for HT hypothyroidism, who developed PM and CMV infection simultaneously. To the best of our knowledge, this is the only case report of PM associated with CMV infection in a patient with HT. There were some difficulties in interpreting the examination results and various challenges on managing the complexity of the diseases coexistence for this case. Limited evidence suggests a possible association between PM and HT, between PM and CMV infection, and between CMV infection and HT. Although the literature confirms CMV as a notorious agent for autoimmune diseases, we found only one case report on polymyositis associated with primary CMV infection [15].

The study suggested two potential interpretations of the physiopathology of PM: PM triggered by the indirect role of CMV infection; and viral myositis, which resulted from muscle cell CMV infection. With regard to the second hypothesis, the inflammatory cell infiltrate in muscles found in our patient which are typically found in patients with PM, rule out the presence of viral myositis. Therefore, the first possible explanation which considers CMV infection as a trigger for PM is more likely. Moreover, the lack of the presence of CMV IgM and the IgG seropositivity demonstrates a primary CMV infection in our patient and supports the role as a trigger. As for the possible mechanisms two explanations were proposed: immunological cross-reactivity as a result of molecular mimicry and virus-induced expression of histocompatibility complexes[13].

From the literature search, we found two case reports on the link between PM and HT. Sung and coworkers[10] described the case of a 20-year-old woman who was diagnosed with polymyositis and Hashimoto`s thyroiditis concomitantly and a study by Wang and coworkers [9] presented the case of a 45-year-old woman with hypothyroidism who developed polymyositis. Even though the coexistence of PM and autoimmune thyroid dis-eases (AITD) is not well documented there seems to share a potential common pathogenic mechanism. The potential mechanisms which have been postulated include: (1) common environmental factors such as a drug, a chemical or a virus

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triggering both AITD and polymyositis in genetically susceptible host [9][16]; (2) a genetic link between antithyroid autoimmunity and the susceptibility to autoimmune disease[9][10]; (3) molecular mimicry between PM and disease specific epitopes[10]; (4) cross reactivity of antithyroid antibodies or autoreactive T cells with other organs or other autoantibodies[9][10][16], (5) immunomodulatory effects of antithyroid antibodies[17][18]; and (6) cytokine imbalance(9). Both studies provide evidence that these two diseases may overlap and show that PM diagnosis could precede or parallel hypothyroidism.

Regarding the relationship between CMV and HT, some evidence implies that CMV is a causal agent for thyroiditis[19][13] and other have shown the presence of active CMV replication in patients with HT[12]. Larouche and coworkers(19) reported the case of a 49-year-old immunocompetent women who experienced an episode of cytomegalovirus-induced mononucleosis before developing thyroiditis. In a review, Freeman, R.B [12] states that the CMV replication has been found in many areas of inflammation in several auto-immune diseases including HT, although it gives no answer to the question whether the CMV replication triggers inflammation or vice versa.

Moreover, there is growing evidence that suggests that CMV infection is associated with autoimmune diseases. CMV is part of the herpes virus family, and it is usually acquired in the first few years of life via direct contact with other individuals infected body fluids. After the initial immune response, the virus becomes dormant and may reactivate in cases of diminished immunity. While in most cases the CMV reactivation may be asymptomatic, in many other cases, particularly in immune-compromised people may have severe consequences. However, literature shows that CMV infection plays a critical role in auto-immunity even in immunocompetent individuals. A recent review by Gugliesi and coworkers[20] suggests the existence of an interaction between CMV and the immune system supported by the fact that the viral infection has been found in several autoimmune diseases, such as neurological, enteric disorders and metabolic diseases, and rheumatological diseases in particular. The study also postulates that the documented mechanisms of this interplay include inflammation, molecular mimicry, and nonspecific B-cell activation. Furthermore, based on literature findings, the authors suggest that autoimmune dis-eases and CMV infection reciprocally affect each other. On the one hand, primary or secondary CMV infection can cause persistent type I inflammation throughout the body, which encourages autoimmunity and thus causes autoimmune disorders. On the other hand, autoimmune flares can also trigger CMV reactivation[20][21].

In our case, based on the currently available literature summarized in this report it is reasonable to support the theory of CMV infection as shared environmental causal factor for PM and HT. Additionally, we suggest that the proposed etiopathogenic mechanism of molecular mimicry found as a potential explanation in the relationship between PM and HT and between PM and CMV infection and on the link between CMV and HT is more likely to have caused the overlap over these three diseases. Molecular mimicry is a concept in immunology and autoimmune diseases research that describes the mechanism which is used to explain how the immune system may cause the development of antibodies that attack the self since viruses, bacteria, and their hosts all contain structurally similar or identical antigens. The four different forms of molecular mimicry include: (1) complete identity at the protein level between a microorganism and its host, however the protein is not encoded by the microorganism; (2) homology at the protein level between a microbe and its host, of a protein which is encoded by the microbe; (3) similarity at the level of epitopes or amino acid sequences between the environmental agent or the microorganism and its host; and (4) structural similarities between the microbe or environmental agent and its host. For instance, the human cytomegalovirus (CMV) envelope contains CD13 (aminopeptidase N) molecules, thus presenting the first form of molecular mimicry[22].

This cross-reactivity between self and viral antigens where structural parts of the pathogen such as viral epitopes “imitate” or “stimulate” the molecules of the host, is thought to be responsible for the development or exacerbation of several autoimmune diseases. Yet, there are four criteria that need to be fulfilled in these case include: (1) Similarity between a host epitope and an environmental or microbial agent's epitope; (2) detection of anti- bodies, B or T cells that are cross-reactive with both

epitopes in autoimmune disease patients; (3) the epidemiological connection between the onset of an autoimmune illness and exposure to an environmental chemical or microorganism; and (4) reproducibility of autoimmunity in an animal model after exposure to the environmental toxin, infection with the microorganism, or sensitization with the epitopes[22]. However, testing the fulfillment of the criteria of molecular mimicry was not part of the study's objectives, as this study aimed at presenting a unique case of viral and autoimmune diseases overlapping and shedding light on the potential interpretations of the common etiopathology. Nevertheless, we do not exclude any of the other possible interpretations, leaving the question open to whether CMV infection can play a role as a trigger for autoimmune diseases or not.

In conclusion, our findings suggest a potential interplay between the immune system and CMV. Although there have been significant efforts to study the connection between CMV infection and autoimmunity it is still not well documented if CMV infection induces autoimmune disorders or is a by-product that is associated with the perpetuation of autoimmune diseases. Further research is needed to elucidate this relationship.

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