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Combination of Opportunistic Infections in a Case of Chronic Inflammatory Demyelinating Polyradiculopathy

Kronik İnflamatuvar Demiyelinizan Poliradikülopatili Bir Hastada Fırsatçı İnfeksiyonların Kombinasyonu

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SUMMARY

Cytomegalovirus infections are asymptomatic when they appear in childhood and adolescence. However, cytomegalovirus causes severe infections in immuno-suppressed patients. The virus may lead to primary infections or it may result in secondary infections in the form of reactivation or reinfection when the immune system is suppressed since it may be latent in various parts of the body. Leishmaniasis is transmitted by phlebotomuses and caused by Leishmania, an intracellular protozoon. In visceral leishmaniasis, protozoons caught by macrophages are kept in the reticuloendothelial system. Patients develop hepatosplenomegaly, anemia, leucopenia, and thrombocytopenia due to bone marrow involvement. The disease has a poor outlook in immuno-suppressed individuals and patients receiving immuno-suppressive treatment. Leishmaniasis is endemic in Aegean and Mediterranean regions of Turkey, but sporadic in other regions. A rare case of cytomegolovirus infection accompanied by kala-azar development during treatment with steroids for chronic inflammatory demyelineating polyradiculopathy is reported.

Keys Works: *Kala-azar, Cytomegalovirus, Immunosuppression*

ÖZET

Kronik İnflamatuvar Demiyelinizan Poliradikülopatili Bir Hastada Fırsatçı İnfeksiyonların Kombinasyonu

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Sitomegalovirüs infeksiyonları tüm çocukluk ve ergenik döneminde belirtisiz geçirilir. Ancak bağışıklık yetmezliği olanlarda ağır infeksiyonlara neden olur. Sitomegalovirüs primer infeksiyona veya immün sistem baskılandığında reaktivasyon veya reinfeksiyon şeklinde sekonder infeksiyona yol açabilir. Çünkü sitomegalovirüs vücutta çok çeşitli bölgelerde latens gösterebilir. Leishmaniasis phlebotomus'lar

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tarafından bulaşır ve nedeni hücre içi protozoon olan leyşmanyalardır. Visseral leyşmanyazda, makrofajlarca yakalanan protozoalar retiküloendotelyal sistemde tutulur. Hastalarda hepatosplenomegali, kemik iliği tutulumu nedeniyle anemi, lökopeni ve trombositopeni gelişir. Hastalık immünsüpresif olanlarda ve immünsüpresif tedavi alanlarda kötü seyreder. Leyşmanyaz Türkiye'de Ege ve Akdeniz bölgesinde endemik, diğer bölgelerde sporadiktir. Burada kronik inflamatuvar demiyelinizan poliradikülopati nedeniyle steroid tedavisi almaktayken, kala-azar ve sitomegalovirüs infeksiyonunun birlikte gözlendiği nadir bir olguyu sunmaktayız

Anahtar Kelimeler *Kala-azar, Sitomegalovirüs, İmmünsüpresyon*

INTRODUCTION

Cytomegalovirus (CMV) infection is most commonly subclinical. However, immunocompromised host, primary CMV infection, reactivation, and reinfection are all associated with significant morbidity and mortality. Visceral leishmaniasis (Kala-azar) is a systemic disease characterized by hepatosplenomegaly, fever, weight loss, leukopenia, and ultimately death unless the disease is treated. There is evidence of activation of a latent infection several years after exposure to the parasite under conditions of immunosuppression. A patient being treated with steroid therapy for his primary disease "chronic inflammatory demyelinating polyradiculopathy" and herewith having CMV and Kala-azar is discussed here.

CASE REPORT

A 30-year-old male teacher presented to our outpatient clinic with high fever on 4 July 2012. The patient history revealed that he had been followed in a neurology clinic for Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP) since 14 February 2012 and had initially received treatment with prednizolon 64 mg/day which was reduced gradually. At the time of presentation, the patient was receiving steroids 16 mg/day and had a history of fever lasting for nine days. The fever preceded by shivering three times and lasting for 2-3 hours was accompanied by cough but not sputum when it peaked. Results of a laboratory investigation performed in another centre on 28 June 2012 showed hemoglobin 11 g/dL, leukocytes 3100/mm^3, neutrophils 2100/mm^3, platelets 35.000/mm^3, C-reactive protein 275 mg/L, erythrocyte sedimentation rate 25 mm/hour, alanine aminotransferase 901 U/L, aspartate aminotransferase 859 U/L, and negative serology for salmonella and brucella. Abdominal ultrasonography showed normal results. The patient was referred to our hospital so that etiology of fever could be determined.

On physical examination, the patient had a good general condition, was conscious, and cooperative. His temperature was 39.5°C, heart rate 109/min, respiration rate 22/min, and blood pressure 130/80 mmHg. His skin was pale. On abdominal examination, the traube was closed and the liver extended 2 cm beyond the rib. The other organ systems were normal. The results of blood tests at presentation: hemoglobin 8.5 g/dL, leukocytes 2800/mm^3, neutrophils 1300/mm^3, platelets 14.000/mm^3, C-reactive protein 293 mg/L, alanine aminotransferase 579 U/L, aspartate aminotransferase 609 U/L, albumin 2.1 g, urea 43 mg/dL, creatinine 1 mg/dL. Pulmonary X-ray did not show any abnormalities. Since his temperature increased, three peripheral blood specimens for blood cultures were obtained; however, no microorganisms were isolated. Tube agglutination tests for brucellosis and salmonella were also negative. Due to high liver enzymes, viral markers were investigated. Anti-HAV IgG, anti-CMV IgM, and IgG were positive. Abdominal ultrasonography performed to determine etiology of fever showed no pathologies except that the spleen was 128 mm and the liver was 175 mm. Since anti-CMV IgM and IgG were positive, tests for anti-CMV IgG avidity and CMV PCR were requested. Avidity was 0.655 (cut-off value: 0.2-0.8). CMV PCR was 1060 copies/mL. The patient was diagnosed as CMV infection and ganciclovir 5 mg/kg every twelve hours was initiated; CMV retinitis was not detected. Steroids administered for the treatment of CIDP were withheld for a period of time upon consultation with the neurologists in our hospital. Since his fever persisted, two more specimens were obtained for blood specimens, but no microorganisms were isolated. On the second day of ganciclovir treatment, maculopapular rashes appeared on the trunk and extremities. The rashes, which tended to merge with each other, were thought to be CMV infection related and the treatment was not discontinued. However, the patient had persistent fever on the fourth day of treatment and

pancytopenia became severe. To determine etiology of fever, high resonance computed tomography (HRCT) and abdomino-pelvic computed tomography (CT), bone marrow aspiration and biopsy were performed and autoimmune markers were investigated. The results of marrow aspiration and biopsy were evaluated with hematologists and pathologists. There was bilateral pleural fluid on HRCT and hepatosplenomegaly and cholelithiasis on abdomino-pelvic CT. Autoimmune markers were negative. After bone marrow aspiration preparations were fixated with methanol, they were stained with Giemsa and examined under immersion objective. On the examination, the bone marrow was hypercellular, the number of plasma cells and histiocytes was increased; however, the number of megakaryocytes was decreased and some histiocytes were observed to phagocytose normoblasts (Figure 1). There were also leishmania amastigots, which were observed to be phagocytosed by histiocytes. As a result, the bone marrow was considered as having hemaphagocytic syndrome and leishmaniasis. In addition to ganciclovir treatment, the patient was initiated liposomal amphotericin B 3 mg/kg/day. Pathological examination of the biopsy specimens showed leishmaniasis and hemaphagocytic syndrome (Figure 2). The patient was administered supplementary treatment including erythrocyte, albumin, and thrombocyte suspensions in addition to medical treatment.

The patient did not have fever one week after treatment with liposomal amphotericin B was initiated and hepatosplenomegaly regressed within the second week of the treatment. The rashes started to subside one week after treatment with ganciclovir. The patient had received treatment with ganciclovir for three weeks and liposomal amphotericin B for ten days and was discharged one month after his admission to hospital.

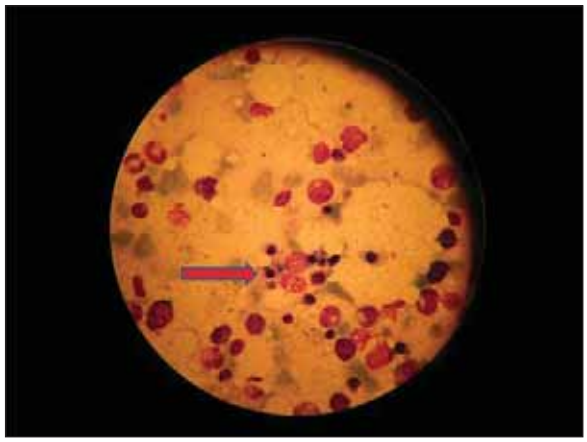

Figure 1. Hemaphagocytosis in bone marrow aspiration smear.

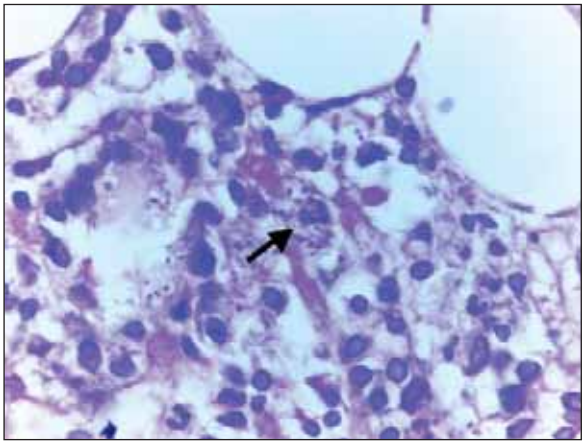

Figure 2. Many Leishman-Donovan bodies seen in the cytoplasm of macrophages (arrow) (H&E stain, X200)

DISCUSSION

The case presented here is interesting in that CMV and Visceral Leishmaniasis (VL) appeared simultaneously and secondary to treatment with steroids for CIDP.

Primary CMV infection is usually asymptomatic in immuno-competent cases. Both primary CMV infection and its reactivation cause important morbidity and mortality in immuno-compromised cases[1]. Exposure to CMV occurs at an early age in developing countries and it has been reported that the seropositivity rate in developing countries is 90% and increases with age, which is true for Turkey as well. However, the sero-positivity rate in developed countries is 15%-65%[2]. Clinical signs of CMV infection are usually fever, pancytopenia and hepatitis and rarely colitis, pneumonia and retinitis.

Although the exact mechanism causing CIDP is not clear, various inflammatory and autoimmune processes are incriminated. In addition, it has been reported that various infectious agents, mostly *Campylobacter jejuni* and CMV, can be responsible for etiology of such diseases especially Guillain-

Barre syndrome[3,4]. The disease is treated with steroids, IVIG, and plasmapheresis. In the case presented here, CIDP was not thought to develop secondary to CMV infection. In fact, the patient was very likely to have experienced the primary disease long before he caught CIDP since the seropositivity rate of CMV infection is very high in Turkey. As a result, the disease was considered as reactivation of the latent infection secondary to steroid treatment. Maculopapular and rubelliform rashes can be seen during the course of CMV infection. They are thought to develop due to an immunological reaction to cellular antigens associated with CMV infection[1,5,6]. In the case presented here, widespread maculopapular rashes appeared on the second day of ganciclovir treatment. Lack of eosinophilia on the peripheral blood smear and normal IgE levels suggested that the rashes were caused by CVM rather than a drug allergy.

VL is a life-threatening, opportunistic infection in immuno-suppressed patients. The disease is accompanied by HIV infection in 25%-70% of the cases in South Europe. In addition, patients receiving corticosteroids and immuno-suppressive treatment, patients with lymphoma, leukemia, chronic hepatitis, sarcoidosis, Chrone's disease and SLE, patients undergoing renal transplantation, and patients with suppressed immune system are vulnerable to VL[7-9]. In these patients, clinical signs are extraordinary, relapses are frequent, and long-term treatment is needed.

Kala-azar can be in the form of primary infection or reactivation of latent infection in patients travelling to or living in regions where the disease is endemic. It is difficult to distinguish reactivated disease from acute newly acquired disease because patients are not screened routinely for leishmaniasis and history of symptomatic infection can be overlooked. It should be kept in mind that the disease can be asymptomatic especially in immune-competent individuals in regions where the disease is endemic.

It is known that glucocorticoids have immunosuppressive features. Immuno-suppression caused by glucocorticoids interferes with defense mechanisms against intracellular microorganism whereby modifying especially T cell activation and proliferation. The disease developed due to intracellular leishmania may show relapses in cases of immune-suppression even if it has been cured. There has been an increasing interest in the literature on reactivation of VL in patients with HIV/AIDS, transplant receivers, and patients receiving immuno-suppressive agents for various conditions[8-10]. The case presented here was living in a region where the disease is endemic and was immune-competent before the diagnosis of CIDP. Although VL could be thought to be a reactivated infection, the possibility of primary infection was not excluded due to lack of a history of VL. FDA approved the use of liposomal amphotericin B 3 mg/kg/day for five days and on the fourteenth and twenty-first days of treatment for VL. It has been reported in several studies that a total dose of 20 mg/kg is appropriate[11]. We have administered liposomal amphotericin B 3 mg/kg for 10 days.

Stained preparations of the specimens from the bone marrow aspiration demonstrated hemophagocytosis syndrome which is characterized by fever, hepatosplenomegaly and cytopenia due to impairment of functions of cytotoxic T lymphocytes and natural killer (NK) cells, activation of macrophages and T lymphocytes, overproduction of proinflammatory cytokins and hemophagocytosis. Secondary hemophagocytosis syndrome is caused by viral, bacterial, protozoal, fungal, and parasitic diseases or malignancy, metabolic diseases, immune deficiency, and collagen tissue diseases. Leishmaniasis is also one of the diseases likely to cause secondary hemaphagocytosis. In fact, it has been reported to result in hemaphagocytosis in 12% of the cases[12,13]. CMV and Ebstein-Barr virus are infectious agents incriminated for hemaphagocytosis. In secondary hemaphagocytosis, the symptoms can subside following treatment of the primary cause. Treatment was also initiated for possible causes and the clinical picture improved.

In conclusion, whatever the cause of the disease is, using immune-suppressive agents can activate latent opportunistic pathogens and the patients living in or travelling to the regions where these pathogens are endemic should be examined carefully for these infections.

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