ADULT-ONSET STILL´S DISEASE AND CYTOMEGALOVIRUS INFECTION

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Abstract

We present a case of a previously asymptomatic 34-year-old man that presented to the emergency department with two weeks of fever, arthralgia of the wrists and knees and sore throat. He was diagnosed with cytomegalovirus (CMV) mononucleosis. The patient remained symptomatic in the 5 following months. After an extensive workup to exclude other clinical conditions, a liver biopsy was performed and CMV hepatitis was diagnosed. He started valganciclovir therapy. Approximately one year after the initial complaints, the patient remained ill and presented clinical criteria compatible with Adult Onset Still´s Disease. The patient had a marked improvement after institution of prednisolone, an effect that has been sustained during the following months.

Keywords: Cytomegalovirus; Adult-onset Still Disease; Cytotoxic Dysfunction.

Introduction

Adult-Onset Still´s Disease (AOSD) is a systemic inflammatory disorder affecting mainly young adults. It typically manifests as a triad of symptoms that include high-spiking fever, a characteristic rash and arthralgias. Fever generally exceeds 39°C and is transient, lasting typically less than 4 hours, and is most commonly daily or twice-a-day in pattern, with the highest temperatures seen in the late afternoon or early evening[1]. Serum inflammatory markers are elevated in laboratory analysis, characteristically with leucocytosis, neutrophilia and high ferritin, with absent reumatoid factor and antinuclear antibodies. AOSD is considered the adult correspondent of Systemic-Onset Juvenile Idiopathic Arthritis (SOJIA). The original Still Disease described by Sir George Frederick Still in 1897 affected young persons. In children this disorder is included in the group of Juvenile Idiopathic Arthritis[2].

The cause of AOSD is unknown. An infectious cause has been postulated, although a definitive agent has yet to be identified[3]. Agents such as rubella, mumps, echovirus 7, cytomegalovirus, Epstein-Barr virus, parainfluenza, coxsackievirus B4, adenovirus, influenza A, human herpes virus 6, parvovirus B19, hepatitis B, hepatitis C, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Yersinia enterocolitica* 3 and 9, *Brucella abortus* and *Borrelia burgdoferi* have all been implicated as triggers in the pathogenesis of AOSD. A link with the presence of certain Human Leukocyte Antigens (HLA) have been described also in patients with AOSD, namely HLA-B17, HLA-B18, HLA-B35 and HLA--DR2[1]. Proinflammatory cytokines such as interleukin (IL) 1, IL-6, IL-18, Interferon Gamma (IFN-γ), Tumor Necrosis Factor (TNF) and Macrophage Colony-Stimulating Factor (M-CSF) are elevated in AOSD and are tough to have a major role in pathogenesis[4]. It seems that the end result is a global reactive syndrome with activation of macrophage, natural-killer (NK) cells and B-lymphocytes, leading to a predominant cell-mediated immune response. Diagnosis of AOSD is one of exclusion, without specific clinical or laboratory anomalies. The most widely accepted criteria set, as presented by Yamaguchi and colleagues, is a compilation of major and minor criteria with the exclusion of infections, malignancies, and other rheumatic or systemic diseases (Table I)[5]. More recently, Fautrel et al have proposed classification criteria utilizing diagnostic markers of serum ferritin and glycosylated ferritin, thought to be more specific for AOSD[6]. Treatment of AOSD is often challenging. Options consist of non-steroidal anti-inflamma-

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Table I. Time evolution of laboratory results

Result/Date	June 2007	December 2007	February 2008	June 2008
White Cells (cell/mm^3)	14.400	18.500	16.440	23.000
Neutrophils (%)	42	79	88	90
Lymphocytes (%)	46	25	29	20
AST (U/L)	70	150	112	40
IgM CMV (UA/ml)[1]	+	+	+	–
Ferritin (ng/ml)	500	1.556	NR[2]	6.400
Immunoglobulins[3]				
IgA	235	171	31	150
IgM	306	113	24	300
IgG	769	729	458	660

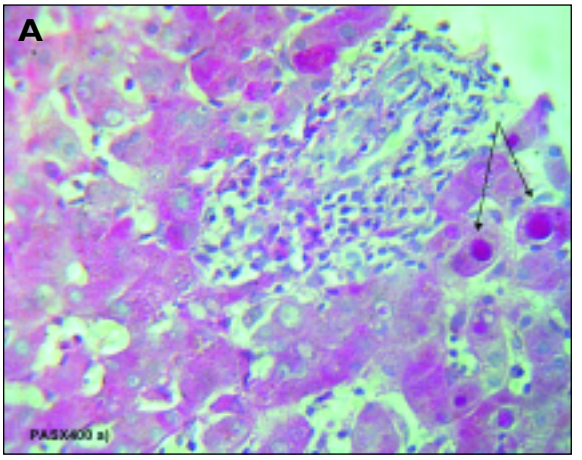
[1] Enzyme immunoassay (EIA). Cutt-off value for positive test is 1.20 UA/ml.
[2] Values not registered.
[3] Normal values (IgA 50 – 400 mg/dl, IgM 50 – 300 mg/dl, IgG600 – 1500 mg/dl.

tory drugs, corticosteroids and other immunosuppressants or immunomodulatory drugs such as methotrexate, gold, azathioprine, leflunomide, cyclosporine and cyclosphosphamide, immunoglobulin and cytokine inhibitors[4].

Cytomegalovirus (CMV) is a herpesvirus that usually causes a mononucleosis syndrome in immunocompetent persons, presenting with fever, leukopenia, relative lymphocytosis, lymphadenopathy, hepatosplenomegaly and myalgia. It is a common infection in all human populations and a large percentage of healthy individuals (50-90%) is chronically infected with the virus. In patients with primary or acquired immunodeficiency, particular with depression of T-cell immunity, CMV reactivation is associated with significant disease in several organs and systems, such as lung, liver, kidney, gastrointestinal tract, central nervous system and heart[7]. Several immune disturbances are described with primary CMV infection, like autoimmune haemolytic anaemia and thrombocytopenia, vasculitis and hypogammaglobulinaemia[8]. In immunocompetent individuals, it is generally assumed that viral replication is suppressed predominantly, but not exclusively, by CD8+ T-cell. A major expansion of specific IFN-γ secreting CD4+ T-cells is now being recognized being associated with primary CMV infection. In acute state, the peak of IFN-γ secreting CD4+ T-cells appears 10 days after CMV DNA is detectable, being followed, 7 days later, by the appearance of immunoglobulin M and immunoglobulin G and, 14 days later, by the appearance of CMV-specific CD8+ T-cells. It seems that both T-cell subtypes must be present to control viral replication and recovery from infection[9]. Primary CMV infection generally doesn't need any treatment. However, CMV reactivation in immunosupressed persons with end-organ disease needs pharmacological treatment with drugs that block viral DNA polymerase, such as ganciclovir, valganciclovir, foscarnet and cidofovir[7].

Case Report

In June 2007 a previously asymptomatic 34-year-old man presented to the emergency department with two weeks of fever, arthralgia of the wrists and knees and sore throat. After one week of an empirically treatment course with amoxicillin-clavulanate (875/125 mg b.i.d) he also experienced a self-limited morbilliform rash. His past history was marked by a Wolf-Parkinson-White Syndrome detected in his youth, treated with ablation of the cardiac accessory pathway. He denied any recent drug exposure or travel. On admission he exhibited a 39ºC tympanic temperature, cervical adenopathies and mild splenomegaly. The remaining physical examination was unremarkable. Analysis showed leukocytosis (14.400 cell/mm^3), absolute and relative lymphocytosis with atypical forms, C-reactive protein 3.53 mg/dL and Erythrocyte Sedimentation Rate (ESR) 21 mm/1sth. There was a slight elevation of transaminases (x 0.5 normal) and a positive CMV



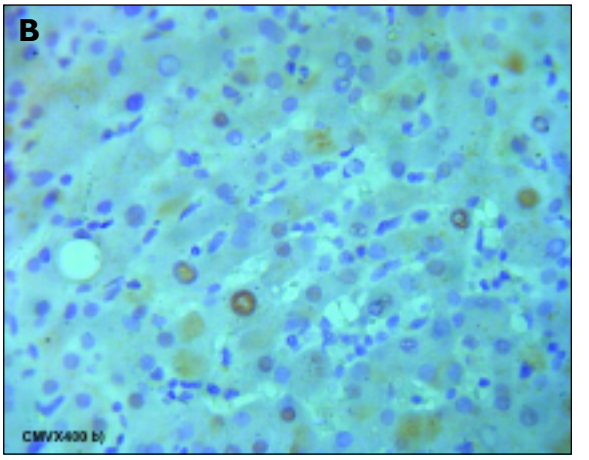


Figure 1. Liver biopsy. **A.** PAS + intranuclear inclusions and periportal inflammatory infiltrate. **B**. Immunohistochemistry with CMV antiserum

IgM and IgG titters (Enzyme immunoassay, cut-off for positive values > 1.2 UA/mL). The search for Hbs and p24 antigens and antibodies against HIV, HCV, HAV, EBV, *Toxoplasma gondii* and Streptolysin-O was negative. CMV-induced mononucleosis syndrome was assumed, and the patient was discharged with acetominophen.

He eventually remained symptomatic in the following months. In October 2007, analytical evaluation showed a persistent leucocytosis, hepatitis (transaminases x 1.5 normal) and high CMV IgM. A liver biopsy was performed. Histological sections in hematoxilin/eosin identified epithelioid granulomas, portal inflammation, nuclear and cytoplasmic inclusions in hepatocytes and Kupfer cells. Immunohistochemistry was compatible with CMV infection (Figure 1). He was started on valganciclovir (900 mg b.i.d). However, after 21 days of therapy, fever remained intermittently.

In February 2008 he maintained elevated titters of CMV IgM and liver enzymes. Cultures of peripheral blood and antibodies to other agents such as *Brucella* spp, *Borrelia* spp and *Coxiella burnetii* were negative. Bone marrow aspirate showed only generalized hyperreactivity without other abnormalities in the main cellular lineages. The culture of blood marrow was negative. Echocardiogram, body computerized tomography scan and upper and lower gastrointestinal endoscopy were normal. Markers for autoimmune/inflammatory diseases such as ANA, ANCA and rheumatoid factors and tumor markers were also negative. Cytometry showed an inversed TCD4+/TCD8+ ratio (ratio 0.52), with CD4+ T-cells 648 cell/µL (30%) and CD8+ T-cell 1240 cell/µL (57%), a low CD19+ B-cell count and a normal CD16+ NK-cell count (141 cell/µl, 7%). IgA, IgG and IgM levels were low (Table I). Tetanus and pneumococcal vaccination resulted in antibody response, excluding Common Variable Immunodeficiency.

In June 2008 he maintained fever and arthralgia of the wrists. He also complained of a light generalized myalgia, predominantly in the cervical muscles. The wrists were found to be painful to palpation, without erythema or edema. Analysis registered leukocytosis (23.000 cell/mm^3) with 90% neutrophils, ESR 77 mm/h and ferritin 6400 ng/mL (Table I). CMV IgM was negative, liver enzymes and immunoglobulins levels were normal. Adult-Onset Still´s Disease was suspected because the patient had clinical and laboratory criteria consistent with Yamaguchi criteria for AOSD (Table I and II). The patient started naproxen 500 mg b.i.d. After two weeks of this therapy, he experienced only a partial improvement of symptoms. His treatment was changed to prednisone 1mg/kg/ /day. There was a marked improvement after institution of this therapy, sustained over the following weeks. Prednisolone was tapered during 3 months to 5 mg q.d, and then were added to the treatment regimen methotrexate (20 mg/week) and naproxen (1 g q.d). The patient has been remained clinically stable with this therapy until the present day.

Discussion

Clinical associations between AOSD and CMV infection can been found in the literature[1,10]. Immu-

Table II. Yamaguchi Criteria for AOSD diagnosis

Yamaguchi Criteria
Diagnosls: 5 Criteria, at least 2 Major
Exclusion Criteria: Infection, Malignancies and Rhematic diseases

Major
Arthralgia > 2 weeks
Fever > 39°, intermittent > 1 week
Typical rash
WBC> 10.000 (> 80% ganulocytes)

Minor
Sore throat
Lymphadenopathy and/or
Splenomegaly
Liver Function Tests abnormal

Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, MiZushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424-30.

nologically, both entities can present abnormalities involving T-cytotoxic dysfunction and high production of IFN-γ. Both are capable of inducing an excessive activation and proliferation of T-cells and macrophages, leading to an overwhelming systemic inflammatory response.

A paradigm of this kind of reaction is the Macrophage Activation Syndrome (MAS, also called Reactive Hemophagocytic Syndrome), an immune "overreaction" that can occur both in patients with AOSD and herpesvirus infection, particular Epstein-Barr virus and CMV. This syndrome was also reported in a patient that was diagnosed simultaneously with a CMV infection and AOSD[11,12]. It is a rare and life-threatening disease characterized by a generalized macrophage phagocytosing of hematopoietic elements, and that usually presents with fever, lymphadenopathy, hepatosplenomegaly, liver dysfunction and coagulopathy. It is now increasingly recognized that MAS bears close resemblance to other closed disorder, Secondary Haemophagocytic Lymphohistiocytosis (HLH), a better-defined entity seen in a heterogeneous group of diseases including infections, neoplasms, haematological conditions and autoimmune disorders.

An immunological link approach MAS, HLH, AOSD, SOJIA and some complicated CMV/other herpesvirus infections: NK and cytotoxic CD8+ T-lymphocyte dysfunction. First, patients with virus-associated HLH showed a very low or absent NK cytolytic activity. Second, it was demonstrated that a quantitative and/or qualitative dysfunction in NK cells result in exaggerated immune response to CMV. In the murine model this leads to expansion of CD8+ T-cell that secrete IFN-γ, an important macrophage and inflammatory activator. Third, it was also proved that CMV has evolved evasion mechanisms to down-regulate or sequester Major Histocompatibility Complex (MHC) molecules, important signals for CD8+ T-cells. This serves as an activating signal for NK cells that trigger their cytolytic activity. It was hypothesised that, after and infection with an agent like CMV in a susceptible host, a fail to kill infected cells and thus, fails to remove antigenic stimulation, leads to a persistent antigen-driven activation and proliferation of T-cells that will cause an escalating cytokine production, leading to macrophage activation[13].

In summary, the authors hypothesized that the combination of genetic susceptibility of the host (possibly a qualitative dysfunction in NK cells and/or general cytotoxic immune status) and a specific viral aggression (CMV infection), produced an aberrant immune response that lead to a chronic inflammatory disorder, AOSD.

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