Hyper IgE in a HIV Positive Patient - Case Report

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Case Report

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Key words: Hyper-IgE Syndrome; HIV infection; cytokines; Th1/Th2; immunology.

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Abstract

Background: Hyperimmunoglobulinemia E Syndrome (HIES) is a primary immunodeficiency syndrome associated with multiple abnormalities. Clinical manifestations of atopic allergy, drug reactions, and increased IgE in serum were previously reported during the course of human immunodeficiency virus (HIV) infection.

Case report: We hereby describe the case of one 63 yrs old male patient with a history of weight loss and diarrhoea, who was previously treated for enterocolitis. He was also treated at the Dermatological Clinic for herpes zoster infection and undiagnosed allergy. Microbiology tests showed presence of Candida and Klebsiella pneumoniae in the patient’s sputum which led to testing and confirmation of HIV/AIDS. After that, Lues was diagnosed and blood sample was sent to our laboratory, to evaluate if this atopic patient was sensitized to beta-lactam antibiotics. The results showed increased level of total IgE for almost 12 times above normal ranges and also allergy to ampicillin was revealed. Highly increased levels of total IgE indicated the possibility for HIE Syndrome in this patient. However the relationship of such findings to the immunologic abnormalities found in patients with HIV is not entirely clear.

Conclusion: In conclusion, this is the first case of HIV positive patient with hyper IgE immunoglobulinemia in the Republic of Macedonia. We addressed the important laboratory findings and actual theories explaining possible association between hyper IgE immunoglobulinemia and HIV/AIDS.

Introduction

Hyperimmunoglobulinemia E Syndrome (HIES) is a rare immunodeficiency disorder with an autosomal dominant (MIM 147060) or recessive (MIM 243700) inheritance pattern, firstly described in 1966 [1].

It is associated with multiple abnormalities, of which the most common are recurrent skin abscesses, pneumonia and high serum levels of IgE [2]. There are facial, dental, and skeletal features which are associated with the dominantly inherited syndrome [3-5].

Two types of HIES have been reported:

Type 1 HIES is inherited in autosomal dominant pattern and displays abnormalities in multiple systems, including the skeletal, dental, and immune systems, whereas type 2 is inherited in autosomal recessive manner and shows abnormalities confined to the immune system. Recently hypomorphic mutations in the signal transducer and activator of transcription 3 (STAT3)
gene were identified. Moreover, a null mutation in the tyrosine kinase 2 (Tyk2) gene, accompanied by susceptibility to intracellular bacteria was identified in type 2 HIES [6]. These findings provide an opportunity to understand better the disease pathogenesis.

Human immunodeficiency virus (HIV) infection is associated with a profound dysregulation of the immune system [7]. In 1988 hyper-IgE-immunoglobulinemia in HIV-positive patients was first described by Lin, who did not investigate the possible immunologic mechanisms of this disorder [8].

The aim of this study was to present the first case of HIV infected individual, accompanied with hyper-IgE immunoglobulinemia in the Republic of Macedonia and address the existing theories about association between HIV and HIES as well as similarities and differences with hyper-IgE immunoglobulinemia.

Case Report

A 63 yrs old man was referred to our clinic with an history of weight loss and diarrhoea, previously diagnosed as enterocolitis. His family history was noncontributory. As for his previous clinical history, he referred herpes zoster infection in 2004 and unspecified allergies. Due to frequent rush and erythema on hands, neck and face, he was hospitalized several times. No skin lesions were visible at the time of visit (Fig.1).

During the last hospitalization, microbiology tests ruled out parasitic infections and showed presence of *Candida* and *Klebsiella pneumoniae* in the patient’s sputum. This led to testing and confirmation of HIV/AIDS test. After that, Lues was diagnosed and therapy of first choice in treatment for Lues is penicillin. Because of his previous allergy history and suspected allergy on penicillin blood sample was sent to our laboratory. Our laboratory findings (Table 1) showed high levels of total IgE-1933 kU/L (normal range 166.7 kU/L) and allergy on ampicillin 0.91 kU/L, class 2 (normal range < 0.35 kU/L, class 0) (UniCAP®, Phadia). Additional laboratory examination showed high levels of IgA 9.22 g/L (normal range 0.7-5.0 g/L), and normal levels of IgM and IgG. The level of immunoglobulin kappa light chain in sera was high (4.16 g/L - normal range 1.7-3.7 g/L), while the level of immunoglobulin lambda light chain and kappa/lambda ratio were normal. The level of transferin was low 0.305 g/L (normal range 2.0-3.6 g/L) and the level of haptoglobin was normal. Laboratory data showed high levels of C reactive protein – CRP 52.5 mg/L (normal range is <3 mg/L) and low levels for a2 macroglobulin (0.775g/L-normal range 1.3-3.0g/L), ceruloplasmin 0.109 g/L (normal range is 0.2-0.6 g/L) and extremely low levels of albumins-18.4 g/L (normal range is 35.0-52.0 g/L) (ProSpec, DADE BEHRING).

Table 1: Laboratory findings in HIV positive patient with hyper IgE.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laboratory finding</th>
<th>Normal range</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IgE (kU/L)</td>
<td>1933</td>
<td>166.7</td>
<td>UniCAP®, Phadia</td>
</tr>
<tr>
<td>ECP (kU/L)</td>
<td>3.18</td>
<td>&lt;13.3</td>
<td>UniCAP®, Phadia</td>
</tr>
<tr>
<td>Trypsin (kU/L)</td>
<td>13.8</td>
<td>&lt;11.4</td>
<td>UniCAP®, Phadia</td>
</tr>
<tr>
<td>Ampicillin (kU/L, class 2)</td>
<td>0.91, class 2</td>
<td>&lt;0.35, class 0</td>
<td>UniCAP®, Phadia</td>
</tr>
<tr>
<td>IgA (g/L)</td>
<td>9.22</td>
<td>0.7-5.0</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>IgM (g/L)</td>
<td>0.843</td>
<td>0.40-0.30</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>IgG (g/L)</td>
<td>10.6</td>
<td>7.0-16.0</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>IgD (g/L)</td>
<td>4.16</td>
<td>1.7-3.7</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>IgG lambda (g/L)</td>
<td>2.03</td>
<td>0.9-2.1</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>IgG lambda (g/L)</td>
<td>2.05</td>
<td>1.3-2.65</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>Transferin (g/L)</td>
<td>0.305</td>
<td>2.0-3.6</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>Haptoglobin (g/L)</td>
<td>1.28</td>
<td>0.3-2.0</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>C1 Inhibitor (g/L)</td>
<td>0.436</td>
<td>0.18-0.39</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>C3 (g/L)</td>
<td>0.449</td>
<td>0.9-1.6</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>C4 (g/L)</td>
<td>0.3</td>
<td>0.1-0.4</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>52.5</td>
<td>&lt;3.0</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>Alpha 1 antitrypsin (g/L)</td>
<td>1.2</td>
<td>0.9-2.0</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>Alpha 1 acid glycoprotein (g/L)</td>
<td>0.777</td>
<td>0.4-1.3</td>
<td>ProSpec, DADE Behring</td>
</tr>
<tr>
<td>Total IgE (kU/L)</td>
<td>1933</td>
<td>166.7</td>
<td>UniCAP®, Phadia</td>
</tr>
<tr>
<td>CRP, C reactive protein.</td>
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</table>

Additionally we made tests for ECP and tryptase levels in sera and they were in normal range.

DNA sample from this patient was stored in the Macedonian Human DNA Bank at the Institute of Immunobiology and Human Genetics, Faculty of Medicine, Skopje, Republic of Macedonia for further investigations [9].

In the last two years we have analyzed 588 patients with suspected allergy on penicillin. We can see on Fig.2 from the ranges of their total IgE, there is a great number of patients which can be suspected as HIE (one that outstands is a person with total IgE level of 30 000 kU/L). This pool of sera and corresponding DNAs (stored at our Institute) represents valuable source for future investigations in the field of primary immunodeficiency disorder HIES.
Discussion

Lange CG et al. reported a case of a 49-year old HIV-1 infected patient with increased serum level of IgE, without clinical symptoms of HIES prior to the patient’s HIV infection. They suggested that hyperimmunoglobulinemia E is related to a cytokine class switch from a TH1 to a TH2 profile along with CD4+ T lymphocytes depletion [10]. Clerici M et al further note that type 1 cytokine production is defective and type 2 cytokine productions is enhanced in HIV-seropositive individuals and that the degree of this disequilibrium might be predictive for progression of HIV infection to the acquired immunodeficiency syndrome (AIDS) [11]. In this perspective, hyper IgE is likely secondary to increased IL-4 production [12].

Highly increased levels of total IgE were observed in this patient. The existing hypoalbuminemia, thrombocytopenia and anemia can be explained with the routine anti retroviral therapy consisting of “Combivir” (combination of Lamivudine and Zidovudine) and “Nevirapine” with which the patient is treated for 2 months. Tuberculostatics were also included in the therapy because of confirmed presence of Mycobacterium tuberculosis.

Hason et al., reported that enfuvirtide (ENF) treatment, which is the first-line anti-HIV drug, is accompanied by an increase of serum IgE [13]. Another study examined whether the ENF had intrinsic capability to direct B-lymphocytes to produce IgE and/or if it could drive CD4+ cells to a Th2 phenotype. The conclusion was that the hyper-IgE production in these patients is associated with the induction of a type-2 phenotype in CD4 T cells [14]. Interestingly, our patient did not receive this drug in the therapy.

Clinical manifestations of atopic allergy, drug reactions, and increased serum levels of IgE have already been described during the course of human immunodeficiency virus (HIV) infection [15, 16]. However, the relationship of such findings to the immunologic abnormalities found in patients with HIV is not entirely clear, though a correlation between the increase of the total IgE level and decrease in the number of the CD4+ lymphocytes has been described [17]. There are studies that show some similarities between HIV-positive patients and those with primary HIES, but also important differences are noted. The hallmarks of these entities are high IgE serum level and hypereosinophilia. The CD4+ lumphopenia in HIV-positive patient and the characteristics of other lymphocyte subsets represent the main distinctive features in comparison with primary HIES [18]. The relationship between elevated serum IgE levels and declining numbers of CD4+ T cells has not been as clearly established in pediatric HIV studies [19, 20].

Seroogy et al. made the first description of a pediatric HIV-infected long-term survivor with primary HIES. Their patient has maintained a normal CD4 count, a low viral load, and primarily production of Th2 cytokines by the CD4+ T-cells. Seroogy et al., also purpose that the high level of total IgE is a factor for poor prognosis in patients with HIV infection. On the other hand, presence of anti-HIV-specific IgE for HIV gp160, p24, p17 and p66 proteins in the sera of HIV positive patient may represent a protective mechanism against HIV replication in the patients [21].

One study in Brazil has shown that pruritic papular eruption can serve as a dermatological marker of HIV infection [22]. Another study finds that pruritic papular eruption may result from the reaction to insect bites occurring while the patient is in the immunodepressed state [23]. According to Milazzo et al., the HIV viral load was increased in patients in whom pruritus was present. They suggested that hyper-IgE and hypereosinophilia are associated with the worst prognosis and that alternations in the type-1/type-2 cytokine profile are prognostically unfavorable [24]. Unfortunately, we couldn’t find any dermatological changes.

Another recently popular model presumes that HIV progression could be associated with a switch from a Th1 to a Th2 phenotype, based on the preferential replication of the virus in Th2 (and Th0) cells [25]. Mechanisms responsible for eventual HIV disease progression and increased viral load over time are multifactorial but are thought to include a shift from Th1 to a Th2...
cytokine profile [26, 27].

Another interesting observation is that elevated serum IgE levels in patients with primary HIES might be independent of Th2 cytokines (predominantly IL-4), suggesting that IgE production in these patients is regulated by another currently undefined pathway [28].

Paganelli shows that in HIV positive patients with absence of CD4+ T cells the hyper IgE and eosinophilia is due to CD8+ T cells that were capable of inducing IgE synthesis. They have shown that both CD8+ T cell lines and the majority of CD8+ T cells clones derived from the patients with AIDS produce IL-4, IL-5 and IL-6 in half of the cases together with interferon â [29].

Recently, one study showed that patients with mutations in STAT3 develop HIES and that they have inadequate Th17 production. Analyses from the peripheral blood of HIV-positive patients have confirmed a decreased Th17:Th1 ratio. This illustrates the role of Th17 cells in controlling pathogens in HIV-positive patients [30].

These models challenges us to further investigate Th1/Th2 switch markers as IL-4, -5, -13 in patient’s serum, the count of CD4+ and CD8+ cells, and also cytokine polymorphism.

We also plan to address the penicillin allergy issue.

In conclusion, this is the first case of HIV positive patient with hyper IgE-immunoglobulinemia in the Republic of Macedonia. We addressed the important laboratory findings and actual theories explaining the association between high IgE levels and HIV/AIDS. Further challenge remains to confirm or reject existing postulates for Th1/Th2 switching.

References


