Recurent Non-Typhoidal Salmonella Bacteremia in a Patient with Interleukin -12p40 Deficiency

Batool Sharifi Mood1, Minoo Mohraz2, Seyed Davood Mansouri3, Roya Alavi Naini1, Hamid Reza Kouhpayeh1, Mohammad Naderi1, Orchidce Filipe Santos4, Guillaume Vogt4, Ariane Chappel4, Jacqueline Feinberg4, Jean Laurent Casanova4, and Taghi Naserpoor5

1 Department of Infectious Diseases, Zahedan University of Medical Sciences, Zahedan, Iran
2 Department of Infectious Diseases, Tehran University of Medical Sciences, Tehran, Iran
3 National Research Institute for Tuberculosis and Lung diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4 Laboratory of Human Genetics of Infectious Diseases, University of Paris Rene Descartes INSERMU550, Necker Medical School, 75015 Paris, France
5 Department of Microbiology, Zahedan University of Medical Sciences, Zahedan, Iran

ABSTRACT

The South eastern region of Iran is an endemic area for salmonellosis. Sometimes bacteremia due to nontyphoidal salmonella occurs but certain patients are at increased risk for recurrent bacteremia. The risk of invasive salmonellosis and recurrent bacteremia is increased in the patients with immunosuppression, especially impaired cell-mediated immunity, lymphoproliferative diseases and in patients with IL-12 deficiency. In recent years, a series of inherited disorders of IL-12-IFN-γ axis have been described that predispose affected individuals to disseminated disease caused by environmental mycobacteria and non-typhoidal salmonella. We report here the first such patient originating from and living in Iran. The patient was a 26-year-old man, suffering from IL-12p40 deficiency and presented with recurrent episodes of systemic salmonellosis. This report indicates that there are patients with inherited defects of the IL-12-IFN-γ circuit in Iran. We recommended to consider this group of disorders in all patients with recurrent non-typhoidal salmonella bacteremia, wherever they are found.

Keywords: Immunologic Deficiency Syndromes; Interleukin-12; Iran; Salmonellosis

INTRODUCTION

Salmonellae are gram-negative, facultatively anaerobic bacilli. Foods of animal origin including meat and poultry eggs or dairy products can become contaminated with salmonella.1-3 Salmonella gastroenteritis is usually a self-limited disease. Although bacteremia develops in less than 5% of all patients with salmonella gastroenteritis, certain patients including; persons with organ transplantation, lymphoproliferative disease, IL-12 deficiency, IL-12 receptor deficiency, IFN-γ deficiency and patients with immunosuppression especially impaired cell-mediated immunity are at increased risk for invasive and recurrent bacterial infections.1,2,4 Disseminated non-typhoidal salmonella infections and severe mycobacterial diseases have previously been reported in the patients with IL-12 deficiency, IL-12 receptor deficiency and in AIDS patients.5,8 Infected macrophages and dendritic cells release IL-12, a heterodimeric cytokine comprising the two subunits p35 and p40. IL-12 plays a crucial role in the development of specific immunity against a number of pathogens.
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of intracellular pathogens including Mycobacterial tuberculosis, Listeria monocytogenes, Salmonella, and Toxoplasma gondii because it stimulates IFN-γ secretion by lymphocyte, which then promotes cell mediated immunity. Deleterious germline mutations in five genes involved in the IL-12-IFN-γ circuit have been found in human patients: IFNγR1, encoding the ligand-binding chain of the IFN-γ receptor (IFN-γR1); IFNGR2, encoding the associated chain of the IFN-γ receptor 2 (IFN-γR2); STAT1, encoding the signal transducer and activator of transcription-1 (Stat-1) in the IFN-γ receptor signaling pathway; IL-12B, encoding the p40 subunit shared by IL-12 and IL-23 and IL-12RB1, encoding the beta 1 subunit shared by the IL-12 and IL-23 receptors (IL-12RB1). The various types of mutation (dominant or recessive, amorphic or hypomorphic) in these five genes define up to ten distinct inherited disorders. All are associated with a rare human syndrome, known as Mendelian susceptibility to mycobacterial disease (MSMD). They are also susceptible to develop non-typhoidal salmonella bacteremia. This report describes a case of IL-12p40 deficiency with recurrent non-typhoidal salmonella bacteremia and repeated episodes of pulmonary tuberculosis. According to our available data, we believe this is the first report of its kind in Iran.

CASE REPORT

A 26-year-old man was admitted to the BooAli Hospital in Zahedan, a city in the Southeast of Iran, on September 2004 because of fever, headache and abdominal discomfort. On physical examination, he appeared ill and toxic with a temperature of 39.4°C. There was multiple tender mass on sternum and in left axilar area. Plain chest X-Ray showed left pleural effusion. The results of laboratory tests are shown in Table 1. The tuberculin test was negative. He had a positive family history for tuberculosis. He was fully vaccinated. Urinalysis was normal. Urine culture was negative but blood and pleural fluid cultures were positive for S. typhimurium. He was treated with ceftriaxon and oral ciprofluxacin for 14 days. In his past history, there was 3 episodes of non typhoidal salmonella bacteremia and 2 courses of treatments for pulmonary tuberculosis at 18 years of age and at the age of 21 for relapse of pulmonary tuberculosis. He was treated 35 days ago for Salmonella typhimurium bacteremia and 4 months ago for Salmonella gallinarum bacteremia. Previous year, he was treated for bacteremia and metastatic abscesses in skin, and pleural empyema due to S. gallinarum. In the second episode of bacteremia following completion of treatment, he received ciprofloxacin 500 mg Bid as chemoprophylaxis for 3 months. Seven days after discontinuation of chemoprophylaxis, the third episode of non typhoidal bacteremia was occurred. In the second episode of bacteremia specific immunologic studies was conducted in a laboratory in Paris (France) on referral blood sample and this laboratory tests revealed deficiencies in IL-12p40 and IFN-γ production. Normal results were obtained in all immunologic test including flow cytometry for CD3+, CD4+, CD8+, CD19+, CD11a+, CD11b+, CD11c+, CD18+, CD28+, CD80+, CD86+, and CD119+ molecules, neutrophil chemotaxis, NBT, serum immunoglobulin and complement levels. Investigation of the IL-12-IFN-γ axis with a recently developed whole-blood assay revealed a lack of IL-12 production by blood cells in response to stimulation with live BCG plus IFN-γ. Sequencing of the IL-12B gene revealed that the patient was homozygous for a missense mutation in IL-12B (g526-528delCt). This mutation exerts its pathogenic effect by creating a premature stop codon in IL-12B (Filipe-santos, et al. in preparation). These data clearly demonstrate that the patient suffers from an autosomal recessive, complete IL-12p40 deficiency, resulting in a lack of IL-12p70 and probably a lack of IL-23.

The production of small amounts of IFN-γ (1-10% normal), induced by cytokines such as IL-18 and IL-27.

Table 1. Laboratory results during hospital admission.

<table>
<thead>
<tr>
<th></th>
<th>First Day</th>
<th>4th Day</th>
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<tbody>
<tr>
<td>WBC /L</td>
<td>26.6x10^9</td>
<td>24.7x10^9</td>
</tr>
<tr>
<td>PMN (%)</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>AST(U/L)</td>
<td>32</td>
<td>47</td>
</tr>
<tr>
<td>ALT(U/L)</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>PT (s)</td>
<td>13</td>
<td>12.5</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>110</td>
<td>83</td>
</tr>
<tr>
<td>PLATELET/L</td>
<td>158x10^9</td>
<td>163x10^9</td>
</tr>
<tr>
<td>ESR /mm/h</td>
<td>70</td>
<td>75</td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PMN: Polymorphonuclear; PT: prothrombin time; WBC: White blood cells

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partly compensates for the lack of IL-12 and IL-23 mediated induction. When the laboratory results received from Necker Laboratory (Paris, France), we recommended the use of IFN-γ but he did not receive this drug. Then two episodes of *Salmonella typhimurium* bacteremia were occurred. Seven days after completion of treatment in 4th episode of non-typhoidal salmonella bacteremia, he expired due to massive hemoptysis in emergency room in another hospital in Zahedan (Figure 1).

**DISCUSSION**

Recurrent non–typhoidal salmonella bacteremia should alert clinicians to immunodeficiency disorders. IL-12 deficiency is a risk factor for acquisition invasive non-typhoidal salmonella infections and repeated episodes of mycobacterial diseases. IL-12, a heterodimeric cytokine comprising the two subunits p35 and p40, produces by macrophage, dendritic cells and other antigen-presenting cells in response to various activators including bacterial stimuli, intracellular parasites and exogenous antigens. Together the subunits form the biologically active p70molecule, which binds to a high-affinity receptor (IL-12R) on natural killer cells, CD4+T helper1 cells and cytotoxic T cells. The ability of IL-12 to activate lymphocytes is mediated by the IL-12R, a heterodimer composed of IL-12RB1 and IL-12RB2 subunits. Binding of IL-12 to the IL-12 R results in activation of Janus kinases Tyk2 and Jak2, leading to tyrosine phosphorylation and DNA binding of Stat4 with subsequent IFN-γ production by T cells. Stat4 is an essential transcription factor for Th1 cell development. IL-12 and IFN-α both activate Stat 4, but with different kinetics. The IL-12RB1 is constitutively expressed on both Th1 and Th2 cells. The IL-12RB2, in contrast, is expressed more strongly on Th1 cells as compared with Th2 cells. The outcome of infection in human infectious diseases is regulated by the Th1 and Th2 cell cytokine patterns. Th1 cells secrete IL-2 and IFN-γ and are generally associated with resistance to intracellular pathogens, whereas Th2 cells secrete IL-4 and IL-10 and are associated with progressive diseases to the same pathogens. Salmonella and mycobacterium tuberculosis are intracellular organisms and patients with IL-12 deficiency can acquire severe diseases and recurrent infections with these organisms. Our patient had four episodes of non-typhoidal salmonella infections and two episodes of pulmonary tuberculosis. At 18 years of age, he was treated for smear-positive pulmonary tuberculosis. Then at the age of 21, he was treated for relapse of pulmonary tuberculosis. He had a positive family history for tuberculosis. Zahedan is a city in Sistan and Baluchestan province in southeast region of Iran that is an endemic area for salmonellosis and tuberculosis. The annual incidence rate for smear-positive pulmonary tuberculosis in Sistan and Baluchestan province has been reported about 41.6 per 100.000 population. Therefore, in this area, persons can be infected with these organisms and IL-12 deficiency is a risk factor for acquisition of severe and recurrent infections because IL-12 plays a key role in shaping the initiation of type 1 helper Tcell (TH1) responses. Also, IL-12 is a potent inducer of IFN-γ from T cells and NK cells. It also has a key role in increasing cell mediated immunity. Therefore in IL-12 deficiency and low level of IFN-γ, many of the patients have a history of recurrent bacterial infections. Repeated episodes of pneumococcal pneumonia with sepsis has been reported by Soichi Haraguchi et al in 1999 in 3-yr-old female patient with IL-12 deficiency. In this patient, the first episode of bacterial infection was shown at 5 weeks after birth and then every two months, she was hospitalized for an invasive bacterial infection. Moreover, two different reports in 1998 by Altare F et al, showed that IL-12 deficiency can be a risk factor for acquisition of severe mycobacterial and salmonella infections. In 2002, Picard C et al, reported 12 patients with IL-12 R deficiency from...
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five groups of kindreds, that had history of recurrent salmonella and mycobacterial infections. There is not any report from Iran about IL-12 deficiency with recurrent non-typhoidal salmonella bacteremia. Our patient had history of recurrent respiratory infection in childhood and also pulmonary tuberculosis and then retreatment for relapse of pulmonary tuberculosis. IL12 deficiency and IL-12R deficiency are not limited to single kindred but our patient had no family history because his family had not been evaluated for IL-12 deficiency. His brother who was 9-years-old, had a history of pulmonary tuberculosis at the age of 6 and repeated episodes of bacterial sinusitis. When our patient was hospitalized for bacteremia and empyema due to S. gallinarum, laboratory tests for humoral and cellular and innate immunity were performed. Deficient in interleukin 12p40 and IFN-γ production was confirmed after specific laboratory evaluations in Paris (France). In conclusion, recurrent non-typhoidal salmonella bacteremia should alert clinicians to immunodeficiency disorders and genetic deficiencies.

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REFERENCES