Chronic Disseminated Salmonellosis in a Patient with Interleukin- 12p40 Deficiency

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Abstract

Interleukin (IL)-12 is composed of p35 and p40 subunit, in this case IL-12p40 deficiency is a rare genetic etiology of Mendelian susceptibility to mycobacterial disease (MSMD). Salmonellosis has been reported in almost half of these patients and mostly present in recurrent extra intestinal form. In this report, we described an 18 month old boy with absence of IL12p40 production suffering from chronic disseminated non-typhoidal salmonellosis. To the best of our knowledge this is the first reported case.

Keywords

Interleukin -12p40 deficiency; Chronic Salmonella; BCGITIS

1. Introduction

Salmonella is a Gram-negative bacillus that may cause acute or chronic asymptomatic infections in immunocompetent children.¹ Infections caused by non-typhoid *Salmonella* (NTS) serovars cause a significant disease burden, with an estimated 93.8 million cases worldwide and 155,000 deaths annually.² NTS serovars, such as *Salmonella enterica*, serovar Typhimurium and serovar enteritidis, cause high rates of bacteremia in an immunocompromised individual.^{3, 4} Vulnerability to *Salmonella* species is a well-known

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feature of Mendelian Susceptibility to Mycobacterial Disease (MSMD; MIM 209950), first described in 1951.⁵

Unlike patients with conventional other immunodeficiencies, patients with MSMD are otherwise healthy and are not prone to experience many atypically severe infections.⁶ The notable exceptions are systemic mycobacterial and NTS, with mycobacterial diseases being the most frequent cause of infections (95.45%). Infections caused by bacillus Calmette-Guerin (BCG) vaccine account for 95% of all mycobacterial diseases and salmonellosis caused 25%.⁷ In patients who did not receive the BCG vaccine, salmonellosis was the only infectious disease found.⁷ In this report, we describe a case of chronic disseminated salmonellosis without documented mycobacterial infection in a patient who had received BCG vaccine.

2. Case presentation

An 18-month-old Saudi boy was referred from Al Gurayyat City, in Northern Saudi Arabia, to rule out primary immunodeficiency. The patient was born by caesarean section due to maternal placenta previa, to healthy and non-consanguineous parents. He received all of his scheduled vaccinations on time, including the BCG vaccine at birth. The patient was well until the age of 3 months. He then developed left axillary swelling that increased in size until the age of 6 months, when it spontaneously ruptured and produced yellowish-reddish discharge. He was seen at a local hospital and given anti-tuberculous therapy (isoniazid and rifampin) for 9 months with no response. He was again admitted to that hospital at the age of 10 and 12 months with septicemia and gastroenteritis, respectively, and treated with ceftriaxone. Family history was significant with a 4 year old brother who had left axillary BCG adenitis at the age of 3 months, and responded well to anti-tuberculous therapy. He was not, however, examined for any immunodeficiencies. The other five siblings were apparently healthy and there was no family history of immunodeficiency. On examination, the patient was found to be unwell, pale, not jaundiced, and afebrile with stable vital signs. His weight was less than the third percentile, length was in the tenth percentile, and head circumference was in the fiftieth percentile. Furthermore, he had a BCG scar on his left deltoid muscle with bilateral cervical, and left axillary lymphadenopathies with no redness, hotness, fluctuation, or discharge. His abdomen was distended with hepatosplenomegaly, but there was no ascites. The patient had no skin rash and the remaining systemic examination was normal.

Investigations revealed a white blood cell count of $13000 \times 10^9/L$, with 43% neutrophils and 48% lymphocytes, a hemoglobin of 7 g/dL, platelets of $229 \times 10^9/L$, C-reactive protein (CRP) of 48 mg/L, and erythrocyte sedimentation rate (ESR) of 148 mm/hr. Serum urea, creatinine, and electrolytes were all within the normal range. Liver enzymes were elevated with aspartate aminotransferase (AST) at 1241 IU/L, alanine transaminase (ALT) at 909 IU/L, and alkaline phosphatase (ALP) at 197 IU/L.

An ultrasound of the neck and left axilla showed multiple enlarged lymph nodes (Figure 1). A Computed Tomography (CT) scan of the chest revealed a large anterior mediastinal necrotizing lymph node that was compressing the cardiac and major mediastinal vessels, and

an infiltration of the lower lobe of the right lung. A CT scan of the abdomen showed hepatosplenomegaly with para-aortic lymphadenopathy and splenic abscesses (Figure 2).

With the initial impression of immunodeficiency with disseminated BCG infection, the patient given isoniazid, rifampin, ethambutol, ciprofloxacin, amikacin, and cefotaxime.

Subsequently, purified protein derivative (PPD) skin test showed no induration. The blood culture was negative. The results of serologic tests for HIV, Epstein-Barr virus, cytomegalovirus, adenovirus, and hepatitis viruses were negative. Left axillary lymph node and splenic biopsies revealed reactive lymphoid hyperplasia with no granuloma. A culture of splenic aspirate grew *Salmonella* group D (non-typhoid) susceptible to ampicillin, cefotaxime, ciprofloxacin, and cotrimoxazole. Ziehl-Neelsen stain was negative for acid-fast bacilli, and mycobacterium tuberculosis complex PCR and culture were negative.

Immunologic studies revealed a normal complete blood cell count, normal immunoglobulin values, normal values of complement components C3 and C4, and normal proportions of lymphocyte subpopulations, including CD3, CD4, CD8, CD16, CD19, CD20, CD45, and CD56 cells. There was a normal response of lymphocytes to mitogens, such as phytohemagglutinin (PHA) and concanavalin A. Furthermore, neutrophil functions, including Burst T test, phagocytosis, and MHC I and MHC II were within normal ranges. Samples were also sent for work up to the Laboratory of Human Genetics at Necker Medical School in France. Whole blood test showed an absence of IL-12p40 production on IFN- γ stimulation (Figure 3). The genomic DNA sequenced indicated a one nucleotide insertion in the IL-12B gene (mutation: 315_316insA) (Figure 4).

The patient showed improvement, and thus discharged on isoniazid, rifampin, ethambutol and ciprofloxacin. Upon follow-up, the patient continued to be unwell and failed to thrive, with generalized lymphadenopathy and hepatosplenomegaly. At the age of 30 months, while he was on same drug regimen, he was readmitted with gastroenteritis and sepsis, septic work-up was negative and was treated with ceftriaxone. Again, he improved and was discharged on the same drug regimen. At the age of 36 months after his parents had discontinued his medications for 45 days, he presented with severe sepsis and was admitted to the pediatric intensive care unit in critical condition requiring intubation and ventilation for a month. Ceftriaxone and amikacin were given and previous medications were resumed. Blood, urine, and stool cultures were negative. However, a cervical lymph node biopsy grew *Salmonella* group D (non-typhoid) with negative mycobacterial workup. Interferon-gamma (IFN- γ) therapy was offered but refused by the parents, and patient slowly improved and discharged on amikacin and cefixime in addition to the previous medications. At an outpatient follow-up 1 month later, the patient showed significant improvement with alertness, weight gain, regression of lymph nodes, liver, and spleen size. Amikacin was discontinued but cefixime and anti-tuberculous therapy was continued. On subsequent outpatient visits, he showed further improvement. Anti-tuberculous therapy were then discontinued after been given for 2 years. Cefixime was continued for another 6 months, then discontinued and the patient was given cotrimoxazole prophylaxis after resolution of all symptoms and normalization of inflammatory markers. Over the next 2 years, he was free of symptoms with normal growth and physical examination.

3. Discussion

The patient inherited a disorder characterized by IL-12p40 deficiency, which is the most common inborn error of cytokines that leads to a rare immunodeficiency. Although rare, this immunodeficiency occurs more than expected due to high prevalence of consanguinity in our society. IL-12p40 deficiency is the first AR cytokine defect identified in humans.⁸ Our patient was found to have an IL-12B gene mutation, 315_316insA. This mutation was previously described in Saudi Arabia patients with Mendelian susceptibility to mycobacterial disease (MSMD, MIM 209950 syndrome).^{9,10} Although the BCG vaccine was given at birth, the patient likely had axillary BCG lymphadenitis, without disseminated BCGosis. Unlike other previously reported cases,⁹ *Salmonella* infection appeared in our patient in a chronic rather than recurrent form. Despite proper management with anti-mycobacterial therapy, which includes ciprofloxacin, that was given for the mycobacterial and *Salmonella* activity, based on *in vitro* susceptibility, there was minimal response. Significant improvement was noticed only with short courses of intravenous third generation cephalosporin, and complete recovery was only achieved with a long course of oral 3rd generation cephalosporin. Decrease *Salmonella* susceptibility to ciprofloxacin and clinical failure despite *in vitro* susceptibility was reported both with and without nalidixic acid resistance.¹¹

The use of interferon gamma in such disease is still debatable, as the results of the studies are conflicting and the evidence of efficacy is not conclusive.^{9,12,13,14} We decide to give our patient benefit of doubt with gamma interferon treatment, however, IFN- γ therapy was refused by parents as the patient improved with conventional treatment.

The patient is currently doing well and attending school, on cotrimoxazole prophylaxis with regular follow-ups. Based on this case, a long course of 3rd generation cephalosporin is recommended until complete clinical and microbiological recovery is achieved. There are many reported cases that have responded well to the combined therapy of Ceftriaxone and ciprofloxacin followed by trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis.^{8,15,16} In some cases of recurrent salmonellosis, antibiotics combined with prolonged prophylaxis have been associated with clinical success.^{15,17,18} In other cases, with or without BCG disease, therapy with antibiotics alone was not sufficient to relieve symptoms of septicemia, and administration of IFN- γ resulted in rapid effervescence and resolution of symptoms.^{8,19,20} Remarkably, more than a quarter of the genetically affected siblings remain asymptomatic. It has been suggested that IL-12 or IL-23 component deficiency are strongly associated with *salmonella* disease, while those with IFN- γ component deficiencies commonly present with mycobacterial disease.^{17, 21}

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Figure 1.
U/S showing left axillary lymph nodes, largest measured about 17 + 12 mm in diameter.

Figure 2.

CT scan of the abdomen: Shows an enlarged liver with a homogenous texture apart from the small lesion seen in posterior right lobe. Multiple variable sizes hypo-dense lesions in the spleen are highly suggestive of an abscess. The scan also shows multiple Para aortic lymph nodes, some of which have central necrosis about 15.8 ± 8.8 mm, and focal lesions that measured 13 ± 16 mm with multiple hypo-dense regions in the right adrenal gland.

Fig. 3. Stimulation with a combination of IL-12 plus BCG increased IFN-F levels in the whole blood of an IL-12p40-deficient patient. Whole blood cells stimulated with live BCG alone or BCG plus exogenous recombinant IFN-F produced no IL-12p40

Fig. 4. Mutated alleles of the IL-12B gene with a 315insA mutation, which is found only in patients from Saudi Arabia.