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Granulomatous skin lesions, severe scrotal and lower limb edema due to mycobacterial infections in a child with complete IFN- γ receptor-1 deficiency

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Abstract

Interferon- γ receptor-1 (IFN γ R1) deficiency is caused by mutations in the *IFN γ R1* gene and is characterized mainly by susceptibility to mycobacterial disease. Herein, we report an 8-month-old boy with complete recessive *IFN γ R1* deficiency, afflicted by recurrent mycobacterial diseases with *Mycobacterium bovis*, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare* and *Mycobacterium fortuitum*. Genetic analysis showed a homozygous mutation (106insT) in the *IFN γ R1* gene leading to complete IFN γ R1 deficiency. In addition, he had atypical mycobacterial skin lesions caused by *M. avium intracellulare* and developed scrotal and lower limb lymphedema secondary to compression of large and fixed inguinal lymphadenopathies. Hematopoietic stem cell transplantation was performed from a matched unrelated donor at 5 years of age; however, he died at 9 months post-transplant. To our knowledge, the patient is the first case with IL-12/IFN- γ pathway defect and severe lymphedema. We have also reviewed and summarized the literature related with IFN γ R1 deficiency.

Keywords

atypical mycobacteria; IL-12/IFN- γ pathway; lymphedema

Genetic defects along the IL-12/IFN- γ pathway have been found in patients with Mendelian susceptibility to mycobacterial disease (MSMD) caused by weakly virulent mycobacteria, such as *Mycobacterium bovis* and nontuberculous environmental mycobacteria, also referred to as atypical mycobacteria, and more virulent *Mycobacterium tuberculosis* [1–6]. These patients are otherwise healthy and are not prone to other unusually severe infections, with the exception of nontyphoidal salmonellosis. In single case reports, other severe infections (*cytomegalovirus* and *varicella zoster virus* diseases, human herpes virus-8-associated Kaposi's sarcoma, listeriosis, klebsiellosis, nocardiosis) have been reported [4,7]. Since 1996, disorders of eight genes, namely *IFN γ R1* (6q23-q24, OMIM

107470), *IFN γ R2* (21q22.1-q22.2, OMIM 147569), *IL12R β 1* (19q13.1, OMIM 601604), *IL12p40* (5q31.1-33.1, OMIM 161561), *STAT1* (2q32.2-q32.2, OMIM 600555), IFN regulatory factor (*IRF8*, 16q24.1, OMIM 601565), *NEMO* (*IKBK γ* , Xq28, OMIM 300248) and *CYBB* (Xp11.4, OMIM 300481), have been associated with predisposition to mycobacterial disease [4,6,8].

The *IFN γ R1* gene has the first human mycobacterial susceptibility gene to be identified [9]. Mutations with both recessive and dominant inheritance patterns result in complete and partial Interferon- γ receptor-1 (IFN γ R1) deficiency, respectively. Casual mutations either abrogate cell surface IFN γ R1 expression leading to loss of IFN- γ responsiveness or prevent IFN- γ recognition due to loss of IFN- γ binding [8–10]. Hematopoietic stem cell transplantation (HSCT) has been proposed as the only curative treatment for complete IFN γ R1 deficiency [11–13].

We report a boy with complete recessive IFN γ R1 deficiency, who had clinical manifestations that have not been reported previously, such as recurrent mycobacterial disease with three different environmental mycobacteria plus mycobacteria tuberculosis, atypical mycobacterial skin lesions, lower limb and scrotal lymphedema probably due to pressure of large and fixed inguinal lymphadenopathies to lymph vessels. We have also reviewed previous publications related with IFN γ R1 deficiency.

Case report

An 8-month-old male patient, born to first-cousin parents (pedigree in Figure 1) was admitted to our hospital with high fever, generalized skin rash and abdominal distension. Results of taking a family history showed he had one healthy brother. He was vaccinated with BCG at 2 months of age. At 7 months of age, he was hospitalized because of prolonged fever and cough. During that period, hepatosplenomegaly, generalized lymphadenomegaly, leukocytosis and elevation of acute phase reactants were determined. Laboratory investigations were as follows: blood, cerebrospinal fluid and urine cultures for bacterial pathogens were found to be negative. Acido-resistant bacilli (ARB) was negative in the fasting gastric liquid. Purified protein derivate (ppd) tuberculin test was 10 mm. *Salmonella* and *Brucella* agglutination tests were negative. Chest x-ray was normal, while computerized tomography of the thorax showed multiple lymphadenopathies, maximum 2 cm in diameter, in the left axillary region; abdominal ultrasonography showed hepatosplenomegaly and hypoechoic lesions in the spleen; left axillary lymph node fine needle aspiration revealed highly positive acido-resistant bacilli with abundant histiocytes; Ziehl-Neelsen stain detected multibacillary, immature, poorly differentiated granuloma formation; treatment with isoniazid, rifampicin and pyrazinamide was started and then the patient admitted to our Pediatric Immunology Department (Izmir, Turkey).

On admission, weight was 8.5 kg (50th percentile), height was 70 cm (50th percentile). Maculopapular rash on the entire body with exfoliation on face and hands was observed. There were multiple, mobile, 1 cm in diameter lymphadenopathies on the cervical, right axillary and inguinal region, and fixed, hard and 3 × 3 cm lymphadenopathy on the left axillary region. Liver was enlarged to 6 cm and the spleen was enlarged to 9 cm. Laboratory examination findings revealed the following: white blood cell count of 13.800/mm³; hemoglobin 9 g/dl; platelet 567.000/mm³; erythrocyte sedimentation rate 108 mm/h; C-reactive protein 12.7 mg/dl; and inverted albumin:globulin ratio with total protein 6.2 g/dl, albumin 2.2 g/dl. Serum hepatic enzymes, ions, urea-creatinine levels were within normal limits. Hematologic malignancies were ruled out by bone marrow aspiration smear. Immunoglobulin levels were very high compared with age-related normal levels (IgG 2620 mg/dl, IgM 389 mg/dl, IgA 406 mg/dl). Lymphocyte subsets and phagoburst test were

normal, excluding severe combined immunodeficiency and chronic granulomatous disease, respectively. Serological investigations for HIV were negative. Left axillary node excisional biopsy was performed and isoniazid, rifampicin, amikacin and clarithromycin with 2-mg/kg/day dose of oral prednisolone therapy was started to cover both *M. tuberculosis* and atypical mycobacterial infection. In the first week of therapy the patient showed significant improvement. Lymph node biopsy revealed granulomatous inflammation and multiple acido-resistant bacilli in histiocytes (Figure 2). *M. tuberculosis* complex was isolated from the bone marrow aspiration material and *M. bovis* was isolated from the lymph node. After 2 months, prednisolone was stopped and the remaining anti-tuberculosis agents were continued. At 11 months, he had severe *varicella zoster virus* infection complicated with pneumonitis. At 3 years of age, he had disseminated lymphoproliferation again.

Mycobacterium avium intracellulare was found to be positive in the fasting gastric liquid. After 6 months, *Mycobacterium fortuitum* was isolated from lymph node. Positive findings such as recurrent mycobacterial infections with different isotypes, severe viral infection, consanguinity, lymphoproliferation, hepatosplenomegaly and hypergammaglobulinemia, led us to study the IL-12/IFN- γ pathway. Plasma IFN- γ level was high (1640 pg/ml). Genetic analysis showed a homozygous mutation (106insT) in the *IFN γ R1* gene leading to complete IFN γ R1 deficiency. As he did not have a HLA-identical family donor, screening for a matched unrelated donor was started.

At 4 years of age, he had remarkable edema on lower extremities (Figure 3). Laboratory examinations revealed hypoalbuminemia. Protein loss in 24-h urine was within normal ranges (3.4 mg/m²/h). Liver functions other than albumin were normal and he did not have gastrointestinal symptoms such as diarrhea, which might lead to secondary hypoproteinemia. On followup, penile and scrotal edema became evident (Figure 3), with multiple, fixed, hard, 2–4 cm in diameter lymphadenopathies on inguinal regions. Edema was considered as the result of compression of big lymph nodes. Later, as the lymphedema progressed, due to extravasation of lymph and loss of plasma proteins, he had secondary hypoproteinemia and began to receive intravenous human albumin regularly. In addition to the treatment of ciprofloxacin and clarithromycin, rifabutin was added as the third antimycobacterial agent. At 5 years of age, the patient had a significant number of pathologies (Box 1). In addition, he had multiple, diffuse, squamous lesions on upper extremities. Histochemical examination of skin biopsy showed irregular epidermal acanthosis, spongiosis, increased dermal vascularity, foamy histiocytes filled with lots of acid-fast staining bacteria with Ziehl–Neelsen stain with foreign-body reacting to keratine, without IgA and C3 deposition (Figure 4). *M. avium intracellulare* was isolated from skin biopsy. Skin lesions had spread across the whole body over time, despite regular and continuous antimycobacterial treatment (Figure 3).

Box 1

Positive pathological findings of the patient

- Recurrent mycobacterial infections beginning at the age of 6 months (*Mycobacterium bovis*, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare* and *Mycobacterium fortuitum*)
- BCG-osis during infancy
- Severe *Varicella zoster virus* infection
- Consanguinity: born to first-cousin parents
- Diffuse lymphoproliferation and hepatosplenomegaly

- Laboratory findings: hypergammaglobulinemia, elevated acute phase reactants, inverted albumin:globulin ratio, a homozygous mutation (106insT) in *IFN γ R1* gene leading to complete IFN γ R1 deficiency
- Atypical mycobacterial skin lesions caused by *M. avium intracellulare*
- Scrotal and lower limb lymphedema

HSCT was performed from matched unrelated donor at 5 years of age. The patient received fludarabine, busulfan and anti-timosit globulin for non-myeloablative conditioning regimen and cyclosporine A and mycophenolate mofetil for graft-versus-host disease prophylaxis. The median percentage of donor T-cell chimerism at post-transplantation was 100% on days 33 and 60. Lymphedema on lower extremities and diffuse cutaneous atypical mycobacterial lesions did not recover after HSCT. In the ninth month after his transplant, the patient was admitted to the emergency department with fever, desquamation and echymotic skin lesions on scrotum and drowsiness of 24-h duration. Despite urgent aggressive treatment for septic shock, the patient died 8 h after admission. Post-mortem results of bacteriologic cultures taken at admission revealed *Pseudomonas aeruginosa*.

Discussion

Herein, a Turkish patient with complete recessive IFN γ R1 deficiency, presented with recurrent mycobacterial infections beginning from infancy, developed progressive lymphedema of the lower extremities and diffuse refractory cutaneous atypical granuloma-like lesions, underwent a successful HSCT from a matched unrelated donor and died after a septic attack was reported.

In 1995, six children who appeared to have an autosomal recessive familial immunologic defect predisposing them to infection with a range of mycobacteria were reported [9]. They presented with fever, weight loss, lymphadenopathy and hepatosplenomegaly. Different types of mycobacteria (*Mycobacterium fortuitum*, *M. chelonae*, and four strains of *M. avium intracellulare* complex) were isolated. Treatment with multiple antibiotics failed to eradicate the infection, although treatment with IFN- γ was associated with improvement. In 1996, Newport *et al.* identified four children with severe mycobacterial infections who had a mutation in the gene for IFN γ R1 leading to the absence of receptors on cell surfaces and a functional defect in the upregulation of tumor necrosis factor α by macrophages in response to IFN- γ [9]. In the same year, Jouanguy *et al.* presented a Tunisian girl with IFN γ R1 deficiency and fatal BCG infection [10]. With these reports, IFN γ R1 deficiency was identified as the first etiology of MSMD and has been found to be the second most common etiology of MSMD [9,10]. Most recessive IFN γ R1 deficiencies result in complete loss of cellular responsiveness to IFN- γ , due to mutations that preclude expression of IFN γ R1 on the cell surface or recognition of the ligand IFN- γ [8]. In complete recessive IFN γ R1 deficiency, patients have a more severe phenotype than those with dominant partial deficiency, including earlier onset, increased number and severity of infections and decreased survival [5,6,8]. The patient presented in our report had complete recessive IFN γ R1 with severe phenotype.

Disseminated BCG infection is a typical clinical presentation in patients with an inherited disorder of the IL-12/IFN- γ axis, as BCG, an attenuated strain of *Mycobacterium tuberculosis*, is often the first pathogen to which patients are exposed. Since 1921, BCG vaccination has been employed to immunize newborns routinely in most regions of the world [14]. BCG prevents severe forms of childhood tuberculosis, including miliary tuberculosis and meningitis in particular. However, in rare cases, BCG vaccination results in

disseminated infection involving lymph nodes, lungs, kidney, spleen and other organs. Such infections are referred to as BCG-osis and are considered to be the most serious complication of BCG injection, with a high mortality rate [15,16]. BCG-osis invariably indicates the presence of an underlying impaired immunity, such as severe combined immunodeficiency, chronic granulomatous disease, complete DiGeorge syndrome, HIV infection or genetic defects along the IL-12/IFN- γ axis [17]. In countries with country-wide BCG vaccinations, the first manifestation of complete IFN γ R1 deficiency is usually a BCG infection [8,13]. Our patient was vaccinated at 2 months of age with BCG and later he was found to be positive for *M. bovis* (isolated from lymph node), presenting all signs of BCG-osis.

Dorman *et al.* reported on 60 patients with IFN γ R1 deficiency, 22 of them had recessive complete and 38 had dominant partial deficiency [8]. The overall prevalence of mycobacterial disease was 95% in their cohort. *M. avium* complex was the most commonly isolated opportunistic pathogen in both groups. *M. tuberculosis* was isolated in only one recessive complete IFN γ R1 patient, who was also from Turkey. Despite continuous antimycobacterial prophylaxis, our patient experienced multiple mycobacterial infections with different types of mycobacteria (*M. bovis*, *M. tuberculosis*, *M. avium intracellulare* and *M. fortuitum*).

Opportunistic viral infections, such as *cytomegalovirus*, *herpes simplex virus*, *varicella zoster virus*, respiratory syncytial virus and parainfluenza virus type 3, are reported in patients with IFN γ R1 deficiency [8]. In the report from Dorman *et al.*, 13 out of 60 patients had varicella infection [8]. Our patient had also experienced severe varicella infection with diffuse vesicle formation and interstitial pneumonia.

Cutaneous atypical mycobacterial granuloma, disseminated cutaneous squamous cell carcinoma and cutaneous leukocytoclastic vasculitis have been reported in patients with IL-12/IFN- γ pathway defects [18–20]. Our patient had cutaneous atypical mycobacterial granulomatous lesions, caused by *M. intracellulare*, all over the body, refractory to all known antimycobacterial agents.

Lymphedema is the result of protein-rich interstitial volume overload, secondary to lymph drainage failure. It often occurs in the lower extremities, because of the low number of alternate lymph pathways for drainage. Lymphedema occurs when there is an inherent defect within the lymph-carrying conduits, termed primary lymphedema, or whenever acquired damage arises, termed secondary lymphedema. Secondary lymphedema of the lower extremities is a rare entity in pediatric population. It is a chronic, progressive condition which reduces the quality of life. It may be caused by damage to lymphatic system or pressure to lymphatic system from tumors, scar tissue after radiation therapy, surgical removal of lymph nodes, trauma or infectious disorders such as filariasis [21,22]. Hoda *et al.* [23] had reported two cases with tuberculous lymphedema in 1974, one presented with elephantiasis and the other with unilateral lymphedema. To date, few cases with primary immunodeficiency and lymphedema have been reported. These have disorders in the Nf- κ B signaling pathway such as X-linked osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia and immunodeficiency (OL-EDA-ID) [24–26]. Additionally, cases with yellow nail syndrome, which is a rare disease characterized by yellow nails associated with lymphedema and chronic respiratory manifestations, have been reported to have T- and B-cell immunodeficiency [27]. For the differential diagnosis of our patient, we excluded systemic (congestive cardiac failure, renal failure, protein-losing enteropathy) and local causes (deep vein thrombosis, chronic venous disease) of the swollen leg. It was thought to be lymphedema because there was painless swelling, pitting edema, hyperkeratotic, hyperpigmented skin and hypoalbuminemia.

To our knowledge, no case with MSMD and lymphedema has been reported previously. Our patient had severe lymphedema on the scrotum and lower extremities, probably due to compression of multiple, very hard, enlarged and fixed lymph nodes (computed tomography findings), causing hypoproteinemia that needed albumin replacement therapy.

Mycobacterium species had been isolated from the lymph nodes and it was obvious that the cause of lymphadenitis was mycobacteria. The other reason for this lymphedema may be increased capillary permeability due to chronic generalized skin inflammation. It is difficult to know the exact reason, because lymphangiogram and/or lymphoscintigram were not available during hospitalization. Lymphedema responded partially to albumin treatment and some compression garments.

The prognosis of complete recessive IFN- γ R1 deficiency is poor, with less than 20% surviving to 12 years of age [8,13]. HSCT has been proposed as the only available curative treatment [11,28]. Nine patients have received 12 HSCTs from family donors with 50% survival. Moilanen *et al.* had reported a 9-year-old girl with severe IFN γ R1 deficiency, treated by using an unrelated donor for the first time [13]. She was noted to have no signs of active mycobacterial infection at the time of HSCT and thereafter. Our patient had diffuse cutaneous mycobacterial lesions at the time of HSCT. These lesions disappeared for a short time after engraftment, but relapsed again 3 months after HSCT. Although full donor chimerism, HSCT was found to be inefficient for cutaneous findings and lymphedema.

In conclusion, defects in the IL-12/IFN- γ pathway must be considered in patients with disseminated or recurrent mycobacterial infections and in patients with severe viral infections, especially in countries where BCG vaccination is part of the national health program. It must be kept in mind that these patients may develop granuloma-like skin lesions and severe lymphedema. HSCT must be applied at the earliest time before developing organs are damaged.

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Executive summary

Background

- Genetic defects along the IL-12/IFN- γ pathway have been found in patients with Mendelian susceptibility to mycobacterial disease.
- Herein, we report an 8-month-old boy, born to first-cousin parents, with complete recessive IFN γ R1 deficiency, afflicted by recurrent mycobacterial diseases with *Mycobacterium bovis*, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare* and *Mycobacterium fortuitum*.

Case summary

- The patient had the following pathologies:
 - Recurrent mycobacterial infections beginning at the age of 6 months (*M. bovis*, *M. tuberculosis*, *M. avium intracellulare* and *M. fortuitum*);
 - BCG-osis during infancy;
 - Severe *Varicella zoster virus* infection;
 - Diffuse lymphoproliferation and hepatosplenomegaly;
 - Hypergammaglobulinemia, elevated acute phase reactants, inverted albumin:globulin ratio, a homozygous mutation (106insT) in the *IFN γ R1* gene leading to complete IFN γ R1 deficiency;
 - Atypical mycobacterial skin lesions caused by *M. avium intracellulare*;
 - Scrotal and lower limb lymphedema, due to compression of inguinal, multiple, hard, enlarged and fixed lymph nodes;
 - Hematopoietic stem cell transplantation was performed from matched unrelated donor at 5 years of age.
- The patient died at 9 months post-transplant due to septic shock.

Discussion

- Defects in the IL-12/IFN- γ pathway must be considered in patients with disseminated or recurrent mycobacterial infections and in patients with severe viral infections.
- These patients may develop granuloma-like skin lesions and severe lymphedema.
- Hematopoietic stem cell transplantation must be applied at the earliest time before developing organs are damaged.

Figure 1. Pedigree of the patient
The arrow shows the proband (i.e., the patient).

Figure 2. Histopathologic findings of axillary lymph node biopsy

(A) Foamy histiocytes filled with lots of acid-fast staining bacteria; Ziehl–Neelsen stain (×100). (B) Lymph node and surrounding soft tissue were effaced with lots of foamy histiocytes, plasma cells, few neutrophils, with many capillary vessel proliferations, but without apparently formed granulomas; hematoxylin and eosin stain (×20).

Figure 3.
Granuloma-like skin lesions all over the body and scrotal edema of the patient.

Figure 4. Histopathologic findings of skin biopsy

(A) Dermal mixed cellular infiltration with lots of histiocytes; hematoxylin and eosin stain ($\times 10$). (B) Foamy histiocytes filled with lots of acid-fast staining bacteria; Ziehl–Neelsen stain ($\times 10$).