Disseminated Mycobacterium fortuitum infection in a young girl with IFN-γR1 defect masquerading as histiocytosis

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Δισσεμινατεδ*Μψςοβαςτεριυμ φορτυιτυμ* ινφεςτιον ιν α ψουνγ γιρλ ωιτη*ΙΦΝ-γP1* δεφεςτ μασχυεραδινγ ας ηιστιοςψτοσις

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Disseminated *Mycobacterium fortuitum* infection in a young girl with *IΦN-γP1* defect masquerading as histiocytosis

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To the Editor,

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare inborn error of immunity (IEI) of interferon-γ (IFN- γ) and interleukin 12-23 (IL12-23) pathway with predisposition to weakly virulent mycobacterial infections (*Mycobacterium bovis* and environmental non-tuberculous mycobacteria) and intramacrophagic organisms like bacteria (typhoidal and non-typhoidal Salmonella, Listeria, Klebsiella etc.), fungus (Histoplasmosis, coccidiomycosis, paracoccidiomycosis, candida) and parasites (toxoplasma, leishmania) (1). While Bacille Calmette-Guérin (BCG) vaccine related complications were initially reported in 1951, first gene associated with MSMD (*IΦNγP1* defect) was discovered in 1996 (2). Till date, 18 different gene defects and 250 mutations have been reported in patients with MSMD (*IΛ12Pβ1* defect is the most common) (2).

Clinical manifestations may vary from early onset, fatal, disseminated mycobacterial disease to late onset, localized, less severe mycobacterial infection that may remain clinically silent for long duration (1,2). This variation in clinical presentation depends on the specific gene involved and can be explained by incomplete penetrance. Clinical spectrum of MSMD can be divided into two main classes- (1) Isolated MSMD (mycobacterial infection as the predominant manifestation) and (2) Syndromic MSMD (presence of mycobacterial as well as non-mycobacterial infections) (2). In countries where tuberculosis is endemic, suspicion and diagnosis of MSMD has far reaching effects (1). Unrestrained infection at times can lead to atypical manifestations such as macrophage activation syndrome or vasculitis (1). Although uncontrolled mycobacterial infection and abnormal T cell function can act as triggers for hemophagocytic lymphohistiocytosis, it is considered as an uncommon presentation of MSMD (3). A predominant histiocytosis like presentation because of chronic mycobacterium infection has rarely been reported in children with MSMD (4). This may create a diagnostic conundrum form the treating physician. Herein, we report one such case.

A 3-year-old girl presented with abdominal distension for 1-year along with multiple neck swellings, intermittent fever and progressive pallor for 3 months. She was given anti-tubercular treatment for 3 months prior to coming to us. Her elder brother had died at the age of 3 months due to pneumonia. However, his medical records could not be retrieved.

On examination, she had pallor, generalized lymphadenopathy, eczematous skin rashes, tachypnea and spleno-hepatomegaly (spleen reaching nearly up to umbilicus). Laboratory investigations showed anemia and thrombocytopenia with elevated inflammatory markers[**Table 1**] . Infective work up including tuberculosis, kala-azar, cytomegalovirus and HIV came negative. Serum beta-D glucan was within normal limits [**Table 1**] . Contrast enhanced computed tomography showed patchy consolidation with ground glass opacities in dependent region of both lungs. Fine needle aspiration cytology from lymph node showed granulomatous inflammation and acid-fast bacilli (AFB) stain was negative. Immunological work up showed decreased proportion of naïve helper (CD3+CD4+CD45RA+) and cytotoxic T lymphocytes (CD3+CD8+CD45RA+) and increased proportion of memory helper T lymphocytes (CD3+ CD4+CD45RO+). Lymph node biopsy and bone marrow biopsy showed infiltration of mixed histiocytic population without any evidence of malignancy suggesting a possibility of a histiocytic disorder **(Figure 1)** . However, negative CD1a and S-100 stain ruled out Langerhans cell histiocytosis (LCH).

She was initially treated with broad spectrum antimicrobials. However, she continued to have eczematous skin lesions and frequent blood transfusion requirements. Considering a clinical possibility of non-LCH histiocytic disorder, she was initiated on oral prednisolone (2 mg/kg/day) and whole exome sequencing was sent. She showed a brisk clinical response, her rashes subsided and her transfusion requirements reduced.

Whole exome sequencing revealed a homozygous c.201-2A>G splice variant in intron 2 of *IΦN-γP1* gene. This splice variant skips from end of exon 2 to middle of exon 3 and omit bases 201–302. The observed variation has previously been reported in patients with nontuberculous mycobacterial infections with MSMD. Flow-cytometry showed reduced expression of phospho STAT-1 **(Supplementary Figure 1)**and phospho STAT-4 on gated monocytes and decreased IFN-γ receptor 1 expression on activated granulocytes and monocytes**(Supplementary Figure 2)** in the index child compared to control. She was diagnosed to have MSMD and was empirically initiated on anti-tubercular treatment (isoniazid, rifampicin, levofloxacin and ethambutol). Oral prednisolone was gradually tapered and discontinued.

Four months later, she had recurrence of fever, skin rash and size of liver and spleen increased. A lymph node biopsy was repeated from the axilla which grew *Mycobacterium fortuitum* . She was initiated on meropenem, amikacin, cefixime, clofazimine and levoflocxacin as per drug sensitivity pattern. Due to sub-optimal response, she was subsequently initiated on 3 million units of subcutaneous interferon-α (IFN-α) thrice weekly. On follow-up, regression of hepatosplenomegaly and improvement in cytopenia were noted. She is presently being evaluated for hematopoietic stem cell transplantation.

Uncontrolled activation of macrophages and natural killer (NK) cells cause increased production of pro-inflammatory cytokines. This leads to a state of immune dysregulation that affects multiple systems presenting as sub-acute to chronic febrile illness, eczematous rashes, generalized lymphadenopathy, hepatosplenomegaly, pulmonary infiltrations, and lytic bony lesions. Pancytopenia, hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia reflect this hyperinflammatory state (3). Index child had similar multisystemic involvement which made us consider possibilities of histiocytic disorders and initiation of corticosteroids was considered. However, whole exome sequencing suggested a diagnosis of MSMD and subsequently *M. fortuitum* was also isolated form the lymph node biopsy. Histiocytic presentation of MSMD has rarely been reported in literature in patients with both *IΛ-12Pβ1* and*IΦN-γP1* defects (3,4).

Environmental non-tuberculous mycobacteria are one of the signature organisms associated with MSMD. Index child showed growth of *M. fortuitum* from lymph node biopsy. *M. fortuitum* has been previously reported on multiple occasions in patients with complete*IΦN-γP1* deficiency (5). Most reported patients of MSMD with*M. fortuitum* infection are from Turkey, Italy, Greece and Spain. Some of them had associated co-infections with non-typhoidal*Salmonella* or *M. tuberculosis* . Three of them underwent HSCT and 2 of them succumbed to the illness (5). Cephalosporine (cefoxitin, cefixime), aminoglycosides (amikacin, gentamycin) and fluroquinolones (ciprofloxacin, levofloxacin) are used as empiric treatment for *M. fortuitum* . The index child was, however, treated with meropenem, levofloxacin, amikacin, clofazimine and cefixime based on sensitivity pattern.

Interferon alpha has been found to be useful in patients with MSMD who have refractory mycobacterium infection as was also seen in the index case (6). She is presently being evaluated for HSCT.

To conclude, MSMD should be considered in patients with unexplained histiocytic disorders. All attempts should be made to identify mycobacteria in these cases so that targeted therapy can be used. Interferon alpha may be used in patients with *IΦN-γP1* defect to control mycobacterium infection.

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Table 1- Laboratory Investigations

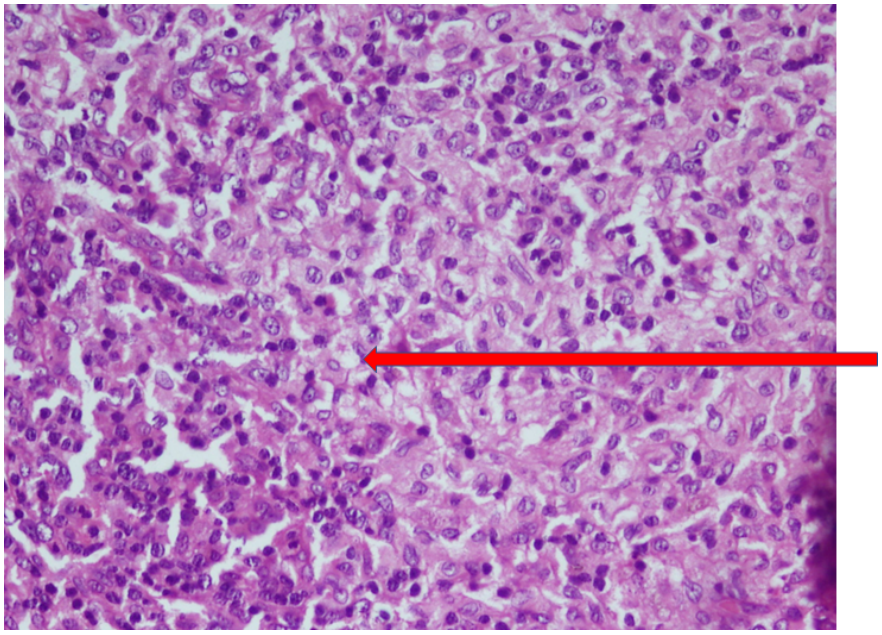
Laboratory parameters	**Case**	**Reference range**
Hemoglobin (g/L)	**57**	115-145
White cell count ($\times 10^9$ /L)	**23.2**	5-14.5
Differential counts	Polymorphs-66% Lymphocytes-23% Monocytes- 5% Eosinophils- 6%	Polymorphs-25-57% Lymphocytes-35-65% Monocytes-0-0.8% Eosinophils- 0-1%
Platelet count ($\times 10^9$ /L)	**30**	150-450
Erythrocyte sedimentation rate (mm after 1st hour)	**28**	< 20
Urea (mg/dL)	18	10-36
Creatinine (mg/dL)	0.26	0.12-1.06
Protein (gm/dL)	6.7	6-8
Albumin (gm/dL)	2.8	3.7-5.5
Globulin (gm/dL)	3.9	2.3-2.5
C-Reactive Protein (mg/L)	**65**	< 6
β-D glucan (pg/mL)	**10**	< 80

Figure legends

Figure 1. Lymph node biopsy showing histiocytic infiltration

Supplementary Figure 1. Reduced Flow-cytometry expression of pSTAT1 on gated monocytes in patients (10.99%) compared to age and sex matched healthy control (34.93%)

Supplementary Figure 2. Reduced Flow-cytometry expression of CD 119 (IFN-γR1) in patients (on lymphocyte-8.79%, monocyte-10.24% and neutrophil-5.13%) compared to age and sex matched healthy control (on lymphocyte-49.02%, monocyte-95.96% and neutrophil-96.82%)



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