IMDDHH: a rare entity or a common masquerader?

ABSTRACT

Inborn Errors of Immunity (IEI) is an extremely rare group of heterogenous disorders which are characterized by predisposition to severe unusual and recurrent infections, severe allergies, features suggestive of autoimmune conditions and sometimes malignancies. We report a two-year-old female child presented to our emergency department with complaints of history of recurrent respiratory infections, recurrent skin infections and recent history of purulent discharge from both the ears. Clinical examination revealed acute otitis media, pneumonia, multiple healed skin lesions associated with soft non-tender hepatomegaly and normal cardiac findings. Elevated hepatic transaminases and hypogammaglobulinemia suggested the possibility of an inborn error of immunity. A whole exome sequencing study performed in the patient established a diagnosis of IMDDHH (Immunodeficiency, Developmental Delay, and Hypohomosyteinemia) by revealing a missense mutation in NFE2L2 gene of chromosome 2q31. Diagnosing such conditions with inborn errors of immunity requires a high index of suspicion combined with a comprehensive knowledge of the structure and function of both innate and adaptive immune system. Recurrent skin and respiratory infections in a growing child belonging to a low-and-middle income country like India is a common clinical scenario encountered frequently in pediatric clinic practice and is often ignored after attributing it to poor hygienic conditions. But with careful history taking and examination, a sub-group of such patients may be isolated with high probability of an underlying IEI, which can later be confirmed by genetic work-up.

Keywords: IMDDHH, Immunodeficiency, Developmental Delay, Hypohomocysteinemia, Recurrent Respiratory infections, Recurrent Skin infections

INTRODUCTION

Inborn Errors of Immunity (IEI) is an extremely rare heterogenous group of disorders which are predominantly diagnosed in the infancy or in the early childhood but may sometimes go unnoticed till late adolescence or adulthood [1]. Nearly 500 such disorders have been identified, most of them caused by single gene mutations and affect the normal immune system development and function. While individually rare, the collective prevalence of these conditions can be as high as 1-5 per 1000 population [2]. Classically characterized by recurrent infections and growth failure, IEIs can have multi-system involvement imparting significant morbidity and mortality to the pediatric population and also are a source of significant financial and emotional burden to the family members. While frequent, severe and unusual infections characterize the classical picture of a child with IEI, specific susceptibility to certain infectious agents, severe allergies, inflammatory processes, features suggestive of autoimmunity and certain malignancies are being reported as the presenting features of such patients [3]. We report a two-year old female child who presented to our department with complaints of severe respiratory and skin infections and was later genetically confirmed to be a case of IMDDHH (Immunodeficiency, Developmental Delay, Hypohomocysteinemia), which is an extremely rare inborn error of immunity with only four cases reported till now in literature.

CASE REPORT

The prepositus is a two-year old female child who presented to the emergency room of our Pediatrics department with complaints of pain in both ears with purulent discharge for previous 10 days associated with high grade fever, cough and progressive difficulty in breathing. On examination the patient was confirmed to have bilateral acute otitis media, the features suggestive of pneumonia and evidence of recurrent skin infections in the past as evidenced by the multiple old scars with hyperpigmentation all over body. (**Figure 1 and 2)**

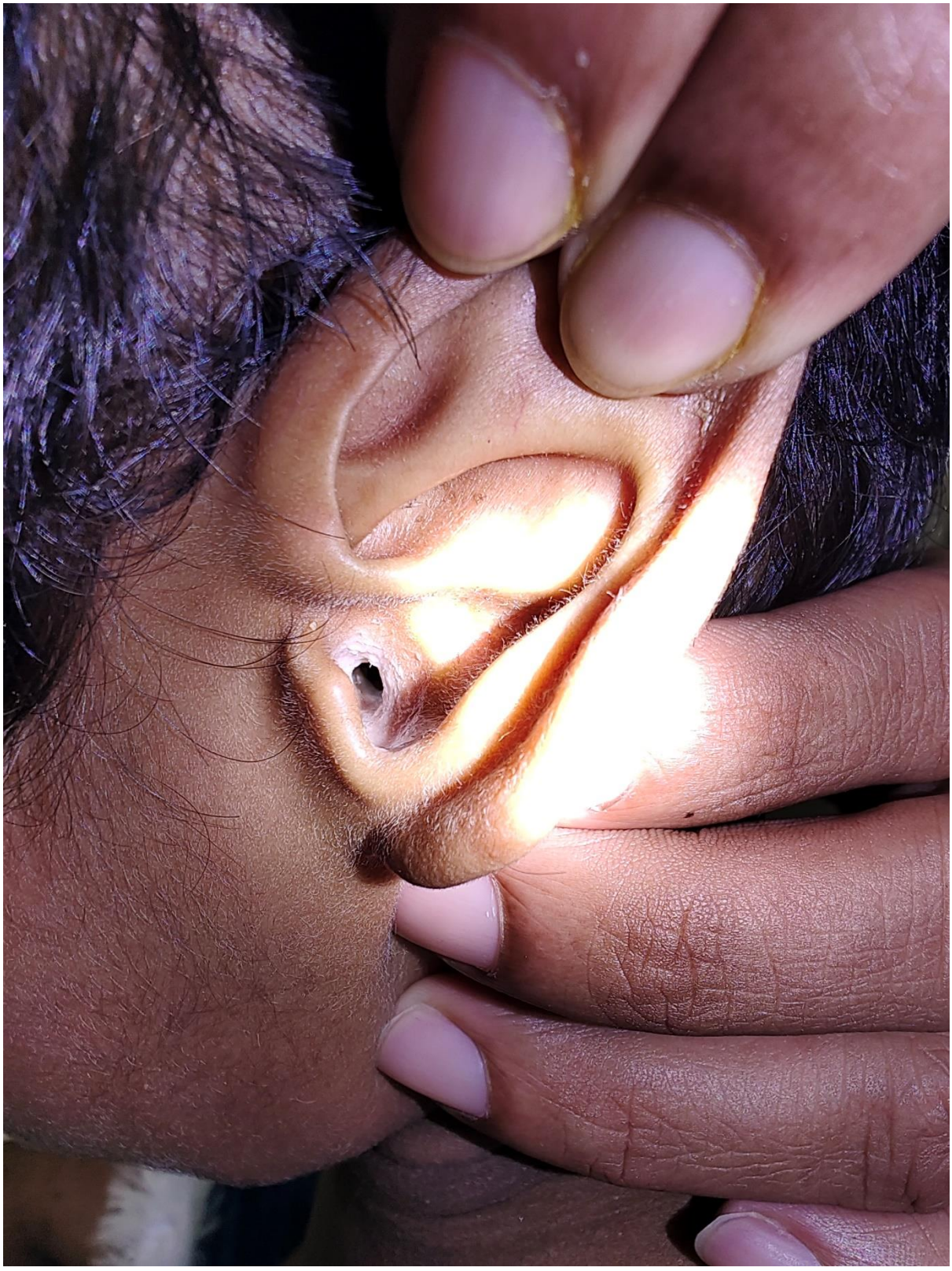

Figure 1: Patient had recurrent episodes of bilateral otitis media

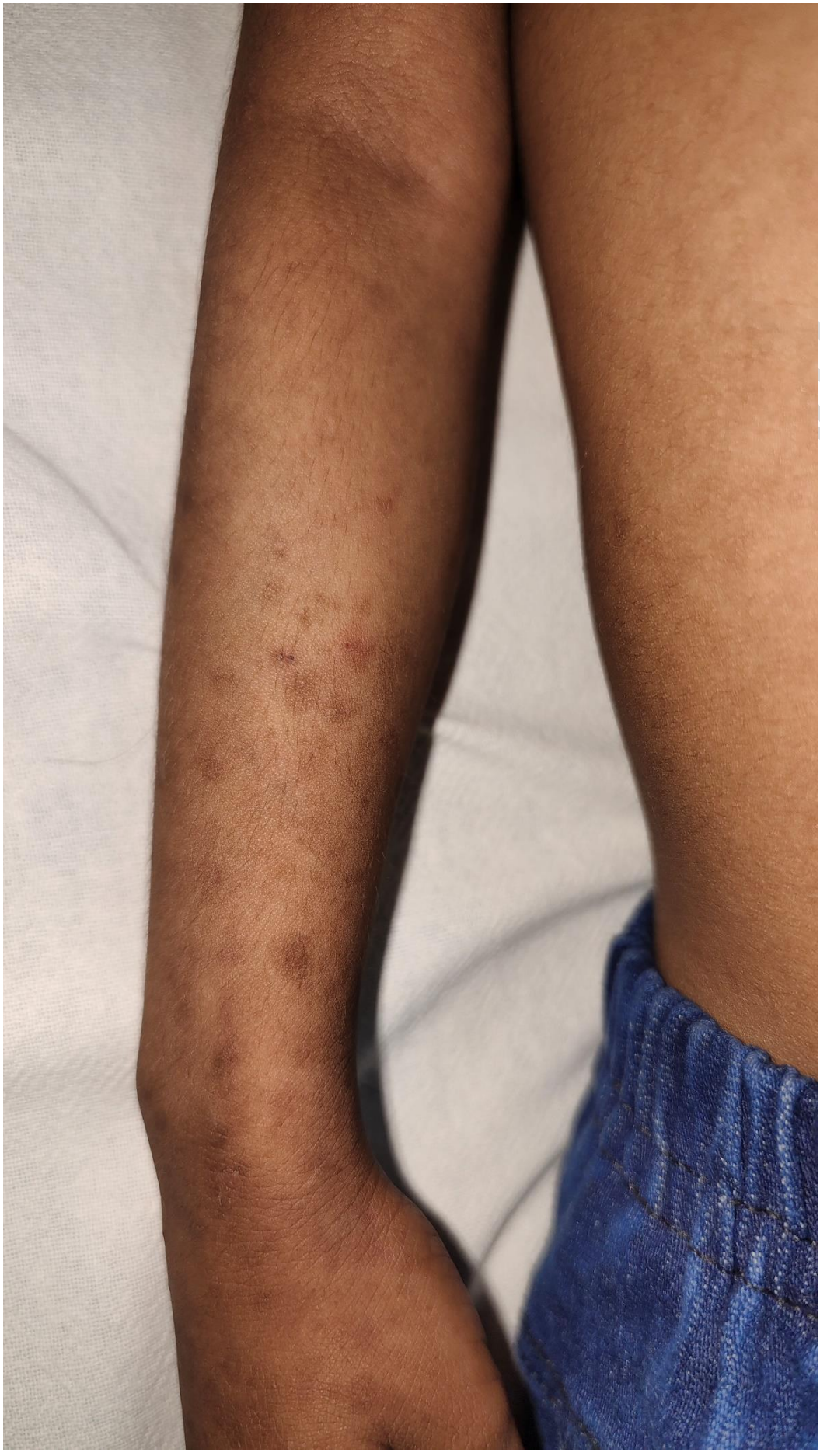

Figure 2: Patient had multiple hypopigmented patches on skin all over the body indicating multiple healed skin infections of past

There was no history of any similar illness in any of the family members, no history of any pregnancy loss or sibling death and immunisation history of the patient was up-to-date for age. There was mild developmental delay in the child in the domains of gross motor, fine motor and language skills. Anthropometry revealed both the weight for age and height for age to be between minus 1 and minus 2 SD (Standard Deviation). The liver span was 8cm indicating hepatomegaly which was soft & non-tender and was also associated with mildly increased transaminase levels. Suspecting the presence of an inborn error of immunity, an immunoglobulin profile of serum was performed which revealed decreased IgG levels. (**Table 1**)

Table 1: Various biochemical paramaters of the patient viz. Hypogammaglobulinemia

Investigation	**Observed value**	**Normal range**
Hemoglobin (g/dL)	10.4	11-13
Total Leukocyte Count (per mm^3)	4,196	4,000-11,000
Total Platelet Count (per mm^3)	2.21Lakh	1.5L-4.5Lakh
SGOT (IU/L)	117	10-40
SGPT (IU/L)	124	10-40
ALP (IU/L)	425	44-147
Total Bilirubin (mg/dL)	0.9	0.2-1
Protein (g/dL)	5.4	6-8
Albumin (g/dL)	3.9	3.5-5.0
Urea (mg/dL)	27	8-40
Creatinine (mg/dL)	0.5	0.6-1.0
IgG level (mg/dL)	125	600-1700

2D ECHO revealed no significant cardiac abnormality. After obtaining consent from parents, a whole exome sequencing study was performed which revealed a missense mutation in NFE2L2 gene at exon 5 (variant c.1244C>G) of chromosome 2q31 (which results in amino acid substitution of Threonine by Serine at position 415) thus confirming a diagnosis of Immunodeficiency, Developmental Delay, Hypohomocysteinemia (IMDDHH), only the fifth reported case in the literature so far. The patient was started on Luteolin and Ascorbic acid tablets and at 6-month follow-up visit, there was no recurrence of Pneumonia and improvement in the skin lesions those were previously present. Patient was doing well. The patient was started on Luteolin and Ascorbic acid tablets and asked to follow-up. At 6-months follow-up, patient continued to have recurrent episodes of lower respiratory tract infections with intermittent hemoptysis and bronchiectatic changes on chest imaging. Patient is being managed by supportive therapy.

DISCUSSION

Immunodeficiency, Developmental Delay, Hypohomocysteinemia (IMDDHH) is an extremely rare multisystem disorder which is characterized by, as the name suggests, immunodeficiency, psychomotor delay, growth failure and hypohomocysteinemia. There is also a variable incidence of congenital cardiac defects and hepatic involvement in the patients affected by this condition. Only four cases have been reported till today in the literature [4].

Nuclear factor erythroid 2 related factor 2 (NRF2) belongs to the Cnc (Cap ‘n’ Collar) family of basic leucine zipper transcription factors that recognizes the Antioxidant Response

Element (ARE) present in the regulator region of the various genes involved in the cellular defense mechanism against several insults such as oxidative stress, infections, toxins and hypoxia [5]. Under the conditions of stress, NRF2 migrates into the cellular nucleus and forms a heterodimer with the small Maf (Musculo Aponeurotic Fibrosarcoma) proteins, which in turn binds to and activates the AREs leading to the activation of the respective target gene [6]. At other times, NRF2 is rapidly inactivated by degradation in 26S proteasome ($T_{1/2}$ = 20 minutes), by virtue of its binding to the KEAP1 homodimers in the cellular cytoplasm. KEAP1, or Kelch-like ECH-associated protein 1, is cysteine rich protein that helps in the ubiquitination of NRF2 by the Cullin-RING E3 ligase complex [7,8]. De novo missense mutations in NFE2L2 affect the binding sites of KEAP1 and lead to accumulation of NRF2 resulting in the increased expression of genes regulated by NRF2 [4].

IMDDHH is caused by heterozygous mutation in NFE2L2 gene on chromosome 2q31 and is inherited in an Autosomal Dominant manner. Huppke at al. have reported 4 unrelated cases between 1 year 8 months and 14 years afflicted with this condition [4]. The patients characteristically have failure to thrive, ultimately leading to short stature. The presence of immunodeficiency leads to recurrent respiratory and skin infections in form of pneumonia, otitis media etc. which may require repeated hospitalizations imparting a severe psychological and financial burden on the family. A work-up often reveals hypogammaglobulinemia, IgA deficiency and sometimes defective NK cell function [4]. The delayed acquisition of fine motor skills and speech development further complicates the life of the affected patients.

Ascorbic acid and Luteolin are two therapeutic options for IMDDHH described in literature so far, as they have been shown to decrease the levels NRF2 and have no serious adverse effects [9]. Ascorbic acid has anti-oxidant effects and can suppress levels of NRF2, and has been utilized in treatment of Imatinib-resistant chronic myelogenous leukemia by virtue of this mechanism of action [10]. Luteolin is a polyphenolic flavonoid and has potent NRF2 inhibitor activity. It is found in high concentrations in celery, parsley and green pepper [11]. Treatment with Luteolin and Ascorbic acid has demonstrated normalization of the hepatic function, reduction in the incidence of respiratory infections and improvement in the scholastic performance of patients with IMDDHH [4].

CONCLUSION

Having a high index of suspicion is extremely important while diagnosing and managing cases suspected of having inborn errors of immunity. Contrary to common belief, the incidence of such conditions may be significantly higher than expected and the low reported incidence can be attributed to the lack of definitive investigations needed to diagnose such rare conditions. A clinical picture characterized by recurrent respiratory and dermatological infections is not uncommon in the pediatric practice and is most often attributed to poor sanitary conditions in a developing country such as India. But when probed upon, such cases may reveal an underlying immune disorder, such as IMDDHH, which can have therapeutic options and can significantly improve the quality of life both of the patient and his/her family.

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