Rare Presentations of Recurrent Pneumonia in Infants with Familial Cold Autoinflammatory Syndromes: A Case Series of FCAS2 and FCAS3

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Abstract

Familial Cold Autoinflammatory Syndrome 2 (FCAS 2) is a rare autoinflammatory disorder associated with mutations in the NLRP12 gene, leading to CAPS-like symptoms. The pathophysiology of FCAS 2 involves dysregulation of the NLRP12 protein, leading to dysregulated activation of the inflammasome complex and subsequent release of pro-inflammatory cytokines. This dysregulated immune response results in recurrent episodes fever and inflammation, often triggered by exposure to cold temperatures. Here, we report two infants with recurrent pneumonia who were diagnosed with FCAS 2 and FCAS 3 without any rash, ocular or other systemic symptoms. The ' clinical course, diagnostic workup, and outcome of both infants, emphasize the need to suspect this rare diagnosis in absence of classical clinical presentations described in literature.

Keywords: Recurrent fever, cold autoinflammatory syndrome, pneumonia

Introduction

Familial Cold Autoinflammatory Syndrome (FCAS) belongs to a group of Cryopyrin associated periodic syndromes (CAPS), caused by dominantly inherited mutations in Nod-Like Receptor Protein (NLRP) genes, particularly *NLRP3*, *NLRP12*, and *PLCG2*.[1,2] These genes play a crucial role in innateimmunity by regulating inflammasome formation and downstream IL-1mediated inflammatory pathways.[2]NLRP12- and PLCG2-associated FCAS (FCAS 2 and FCAS 3) are extremely rare subtypes with currently meager global or Indian literature describing NLRP12- or PLCG2-related FCAS in infancy. The clinical features may be classical like fever, rash, joint disease, ocular and hearing loss in older age but be non specific and overlap with common pediatric conditions such as recurrent viral infections or pneumonia, leading to delayed recognition.[3,4]

We report **two infants presenting with recurrent pneumonia**, who were diagnosed with FCAS, highlighting the importance of considering autoinflammatory syndromes in persistent/recurrent pneumonia or unexplained respiratory symptoms. Early age of symptoms and diagnosis, absence of classical rash, joint disease or ocular manifestations and family involvement make these cases unique.

Case series

Case one

A 7-month-old, late preterm male born out of a non-consanguineous marriage came with complaints of fever, cough and fast breathing for one day during the winter season. Child was diagnosed as pneumonia for the first time at 4 months of age requiring intravenous antibiotics and hospitalization for 10 days. During current episode

infant had tachypnoea (respiratory rate-52/min), hypoxemia (saturation 86% on room air) and rhonchi bilaterally on chest auscultation. Chest X-ray showed consolidation and partial collapse of left lower lobe (Fig 1a). Respiratory viral panel detected H1N1 and thus supportive care and oseltamivir was started. After 48hrs the child developed severe bronchospasm requiring intubation. Child had persistent fever and respiratory distress, repeat nasopharyngeal swab (NP) was sent, which detected pseudomonas aeruginosa. Bronchoscopy done after stabilization of child showed normal anatomy and bronchoalveolar lavage fluid culture reported positive growth of pseudomonas species (sensitive to meropenem, Piperacillin + Tazobactum and colistin) and antibiotics were added according to sensitivity.

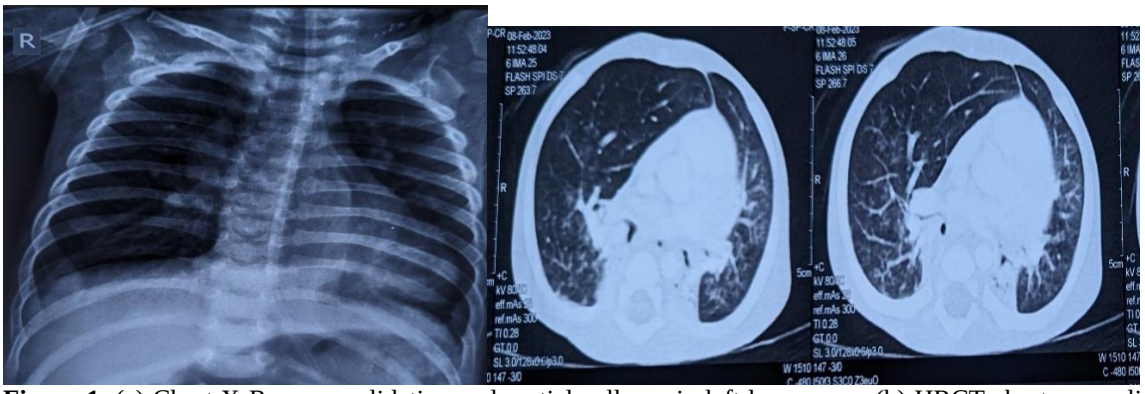

Figure 1: (a) Chest X-Ray: consolidation and partial collapse in left lower zone (b) HRCT chest- consolidation with adjacent patchy ground glass opacity, fibrotic bands in bilateral upper lobes and left lower lobe, few centrilobular nodules, tree in bud appearance.

Common differential diagnosis of recurrent pneumonia in infancy include cystic fibrosis (CF), inborn error of immunity (IEI) and interstitial lung disease (ILD) and were investigated. CF was ruled out as there was no history of oily stools, ear/nasal discharge with normochloremia (Serum chloride: 96mEq/Ldl), absent stool r fat globules, sweat chloride level 33mEq/L(intermediate). IEI was ruled out due to absence of other system involvement and T and B cell profiles (Total Leukocyte count: 11800cells/mm^3, Lymphocytes: 4130cells/mm^3, Neutrophils: 6608cells/mm^3), IgG 639mg/dl, IgM 204mg/dl, IgA 17mg/dl and IgE 7IU/dl; and normal B-cell and T-cells markers CD19, CD20, CD3, CD4, CD8 on flow cytometry. CECT Chest showed left lower lobe collapse, consolidation in right upper and lower lobe, fibrotic bands in both upper lobes (Figure 1b). Despite appropriate antibiotics and supportive treatment after 3 weeks child continued to have fever, expiratory rhonchi and persistent hypoxemia. On reviewing history motherconfirmed increased severity of respiratory symptoms in early morning and exposure to cold. Next-Generation sequencing (NGS) was sent which detected Heterozygous, likely pathogenic mutation in NLRP12(c.2879T>A), and no CFTR related mutations and hence a final diagnosis of FCAS 2 was made. Infant was discharged after 6 weeks of stay and remains under regular follow-up for past 1 year with no further hospitalizations and mild recurrent respiratory symptoms. Parental genetic testing for the NLRP12 variant was planned but limited due to financial constraints.

Case two

A 10-month-old, term male, second in birth order born out of a non-consanguineous marriage presented with complaints of fever, cough, cold with fast breathing for the last 2 days . On examination child had tachypnoea (respiratory rate- 68/min), hypoxia (spO2- 91% on room air) subcostal and intercostal retractions along with nasal flaring. On auscultation child had bilateral rhonchi. Chest X-ray showed bilateral diffuse interstitial prominence with perihilar accentuation (Fig 2a). Child was managed as a case of pneumonia and was started on supportive care and intravenous antibiotics. Child improved and was discharged after 5 days of hospital stay.

The child was again readmitted with similar complaints 45 days post discharge and and treated as pneumonia. Nasopharyngeal swab RT-PCR suggested Human Rhino Virus infection. On reviewing history mother gave history of loose stools that are sticky every 20-40 days since 3 months of age. Child was worked up for cystic fibrosis (negative stool fat globules, (Sweat chloride: 68 mEq/L, 34 mEq/L and 28 mEq/L with normochloremia and normokalemia. IEI was ruled out due to absence of other system involvement and normal laboratory reports (Total Leukocyte count: 14700cells/$mm^{3,}$ Lymphocytes: 5430cells/mm3, neutrophils 7980cells/mm3), normal immunoglobulins (IgG 937mg/dl, IgM 59mg/dl, IgA 30mg/dl and IgE 27IU/dl) and B-cell and T-cells markers(CD19, CD20, CD3, CD4, CD8) on flow cytometry. Bronchoalveolar lavage fluid culture showed no growth. CECT Chest showed patchy consolidation in the bilateral lower zone (Fig 2b). Next-

Generation sequencing (NGS) detected Heterozygous mutation in the PLCG2 gene associated with Familial Cold Autoinflammatory Syndrome 3 and . Infant recovered after each admission and continues under outpatient follow-up for past 1 year. Parental genetic testing for the PLCG2 mutation were limited by financial limitations.

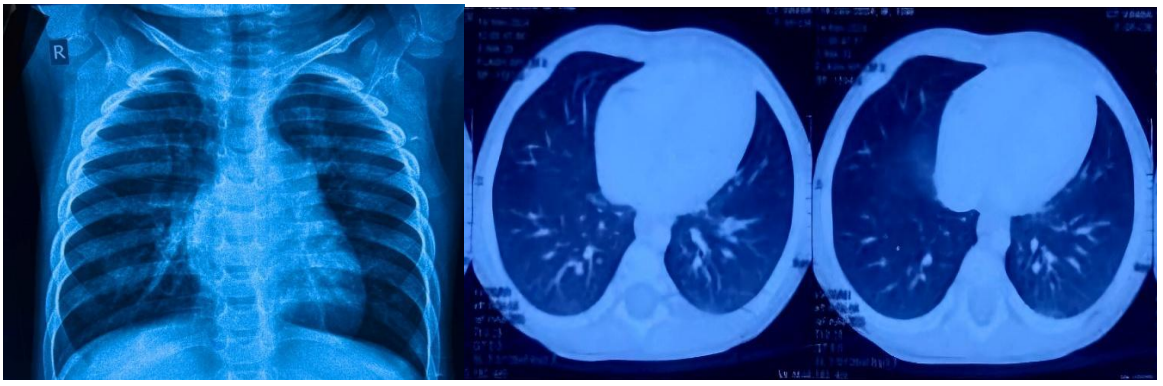

Figure 2: (a) Chest X-Ray: bilateral diffuse interstitial prominence with perihilar accentuation. (b) CECT chest: patchy consolidation, ground glass opacity and bilateral lower zone.

Discussion

NLR Family Pyrin Domain Containing 12 Associated Autoinflammatory Disorder or FCAS was first described in 2008.[5] Nucleotide-binding domain and leucine-rich repeat-containing receptors (NLRs), also known as Nod-like receptors, are a group of highly conserved cytoplasmic pattern recognition receptors.[5] They play important roles in initiating the innate immune response. The NLRP12, also known as monarch-1, is a member of the Caterpillar gene family. NLRP12 is an intracellular protein expressed in bone marrow neutrophils, granulocytes, macrophages and dendritic cells. The role of NLRP12 remains controversial, as it is a negative regulator of inflammation and as an inflammasome.[6] FCAS represents the mildest phenotype within the CAPS spectrum and is classically associated with gain-of-function *NLRP3* mutations (FCAS1).[1]

Although considered rare globally, FCAS typically presents in early infancy, with most patients developing cold-induced urticaria, fever, and arthralgia within the first few months of life. IL-1 blockade remains highly effective in FCAS1, rapidly controlling symptoms and preventing complications such as amyloidosis.[1]In contrast, NLRP12-associated autoinflammatory disease (FCAS2) and PLCG2-associated disease (FCAS3) are exceedingly rare, with markedly fewer published pediatric cases. NLRP12 mutations were first described by Jéru et al,[7] who reported families with neonatal-onset fever, cold-triggered rash, myalgia, and occasional hearing loss.[7] In the Indian cohort by Suri et al., two children with NLRP12 variants were noted to be symptomatic since early infancy.[8] FCAS2 patients typically have recurrent fever (virtually 100% of cases) and cold-triggered urticarial or annular rash, often with musculoskeletal symptoms (arthralgia/myalgia). PLCG2-associated FCAS3 is even rarer. PLCG2 mutations underlie the PLAID/APLAID spectrum and manifest as cold-induced urticaria with elements of immunodeficiency.[4]

Across all forms, infant presentations particularly those mimicking recurrent pneumonia as in our cases, remain rare. In both our cases lack of classical symptoms of rash, muscolo-skeletal involvement and familial affection make the clinical suspicion unlikely, Recurrent respiratory symptoms in our both infants are more commonly relatable to intercurrent infections or other primary lung pathology like cystic fibrosis or interstitial lung diseases. Hence we conclude that in atypical presentations FCAS may be mistakenly attributed to recurrent infectious especially in developing countries like India. Our report adds to the limited global literature highlighting NLRP12- and PLCG2-associated FCAS in infancy from India, emphasizing the importance of early genetic testing and clinical suspicion in infants with unexplained inflammatory episodes or recurrent respiratory illness.

Conclusion

FCAS is a very rare disease with no Indian data and limited data available globally. This diagnosis should be thought of in children with non-specific respiratory symptoms mimicking recurrent pneumonia especially in

cold weather. Genetic studies are diagnostic but may be limited in finance poor settings like India and developing countries.

Disclosure

The authors declared no conflicts of interest. Written consent was obtained from the patient/kin of the patient.

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