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## Brief Communication

## When neonatal inflammation does not mean infection: an early-onset mevalonate kinase deficiency with interstitial lung disease

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## ABSTRACT

Systemic inflammation in neonates is attributable to an infection in almost all cases. When inflammation persists, an autoinflammatory disease should be promptly suspected. We report here a case of mevalonate kinase deficiency (MKD) that presented at birth with mild symptoms and signs suggestive for a perinatal infection, together with the uncommon finding of interstitial lung disease. An extensive diagnostic work-up, performed after ineffective antibiotic treatment, demonstrated high levels of mevalonic acid in urine (7024 mM/M of creatinine, normal value <0.1). Next-generation sequencing showed a rare c.709A > T (p.T237S) homozygous mutation in the *MVK* gene, consistent with MKD. Treatment with anakinra led to a prompt resolution of symptoms and a sharp drop in serum inflammatory markers. The patient is now six months-old, currently undergoing evaluation for hematopoietic stem-cell transplantation. To our knowledge, this is the first case of MKD presenting within the first week of life with interstitial lung disease.

## 1. Introduction

Infections are the most common cause of inflammatory markers elevation and/or fever in the neonatal period [1]. In the first days of life, a systemic inflammatory response may be also due to various non-infectious conditions, such as perinatal asphyxia, meconium aspiration or surgery [2]. However, systemic inflammation usually resolves after adequate treatment during the acute phase of the disease [3].

Among causes of persistent inflammation, autoinflammatory diseases (AIDs) deserve attention because of their possible devastating consequences. AIDs are a group of rare diseases, characterized by the presence of chronic or recurrent systemic inflammation, due to the over-activation and dysregulation of immune response. Few of them can present at birth, as in the case of cryopyrin-associated periodic syndromes (CAPS), STING-associated vasculopathy with onset in infancy

(SAVI), and mevalonate kinase (MVK) deficiency (MKD) [4]. The diagnosis of AIDs requires a high degree of suspicion by neonatologists, given their rarity but also the frequently deceptive, overlapping phenotypes.

Here, we report an early-onset case of MKD, due to a rare homozygous c.709A > T missense mutation (p.T237S) in the exon 8 of *MVK* gene: this case was characterized by a previously unreported interstitial lung disease, a feature overlapping with other AIDs, and a significant, prompt response to the interleukin-1 (IL-1) receptor antagonist anakinra.

## 2. Case presentation

A female neonate born at 37 weeks of gestational age (GA) was transferred to our 3rd level neonatal intensive care unit (NICU) at

Abbreviations: AID, autoinflammatory disease; HIDS, hyper-IgD syndrome; MA, mevalonic aciduria; MVK, mevalonate kinase; MKD, mevalonate kinase deficiency; SAVI, STING-associated vasculopathy with onset in infancy.

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16 days of life (DOL) for persistent raised inflammatory markers in the context of a suspected perinatal infection.

She was born by cesarean section, indicated for anomalies in uterine arterial blood flow, with a birth weight of 2680 g. Parents were of Moroccan nationality, they were second cousins and had another daughter, a healthy four-year-old girl. Maternal history was unremarkable, except for a second pregnancy two years earlier interrupted by fetal death at 36 weeks of GA. Vaccination status of the mother was unknown.

After birth, Apgar score was 10 at 1 and 5 min of life and breastfeeding was successfully started. On DOL 5, skin pallor and mild hypotonia were noted, with no other clinical abnormality: blood tests and cultures were requested for suspected sepsis. The white cell count was  $14,09/\text{mm}^3$  with 42% neutrophils, hemoglobin was 17 g/dL, and C-reactive protein (CRP) was 6.6 mg/dL (normal value for age < 1 mg/dL). Empiric antibiotic therapy (ampicillin plus gentamicin) was started, but blood culture and surface swabs revealed no bacterial growth. Real-time polymerase chain reaction (rt-PCR) for adenovirus, respiratory syncytial virus and rhinovirus on nasopharyngeal swab was negative. Chest X-ray revealed bilateral perihilar peribronchial thickening, with no consolidation, while abdominal and cardiac ultrasound were normal. Lumbar puncture was not performed. On DOL 9, CRP raised to 8.7 mg/dL and antibiotic therapy was switched to vancomycin plus ceftazidime for presumed pulmonary infection. On DOL 15, CRP remained elevated and the baby was transferred to our NICU.

At admission, the patient had normal vital signs, a mild tachypnea, and the previously reported pallor. Hemoglobin was 9.2 g/dL, bilirubin was 0.3 mg/dL, blood arterial lactate, ammonium and glucose were in the normal range. Antibiotic therapy with vancomycin plus ceftazidime was continued and clarithromycin was added waiting to rule out a *Chlamydia trachomatis* infection. Blood, urine and cerebrospinal fluid (CSF) cultures were repeatedly negative for bacteria. A rt-PCR was negative on both blood and CSF for herpes simplex virus 1 and 2, varicella-zoster virus, human herpes virus 6, enterovirus, parechovirus, cytomegalovirus and any bacterial pathogen. Serology for all viruses listed above plus HIV and *Treponema pallidum* was negative. Electroencephalography reported moderate diffuse anomalies of background activity without major abnormalities or electrical seizures.

On DOL 20, the first episode of temperature  $> 38^\circ\text{C}$  was recorded, with a blood culture drawn during febrile peak still negative. Because of worsening tachypnea and persistent abnormal chest X-ray (Fig. 1A), a pulmonary computed tomography (CT) scan was performed. Imaging revealed no congenital malformation but diffuse ground-glass bilateral posterior infiltrates consistent with alveolar-interstitial lung disease (Fig. 1B). A retropharyngeal aspirate was negative for *Pneumocystis* spp. DNA, and three gastric aspirates were negative for *Mycobacterium* spp. DNA. Eighteen hours after CT scan, a palpable maculopapular skin rash appeared on feet and hands, involving both dorsal and palmoplantar surfaces (Fig. 1C-E). The rash vanished spontaneously 24 h later. At

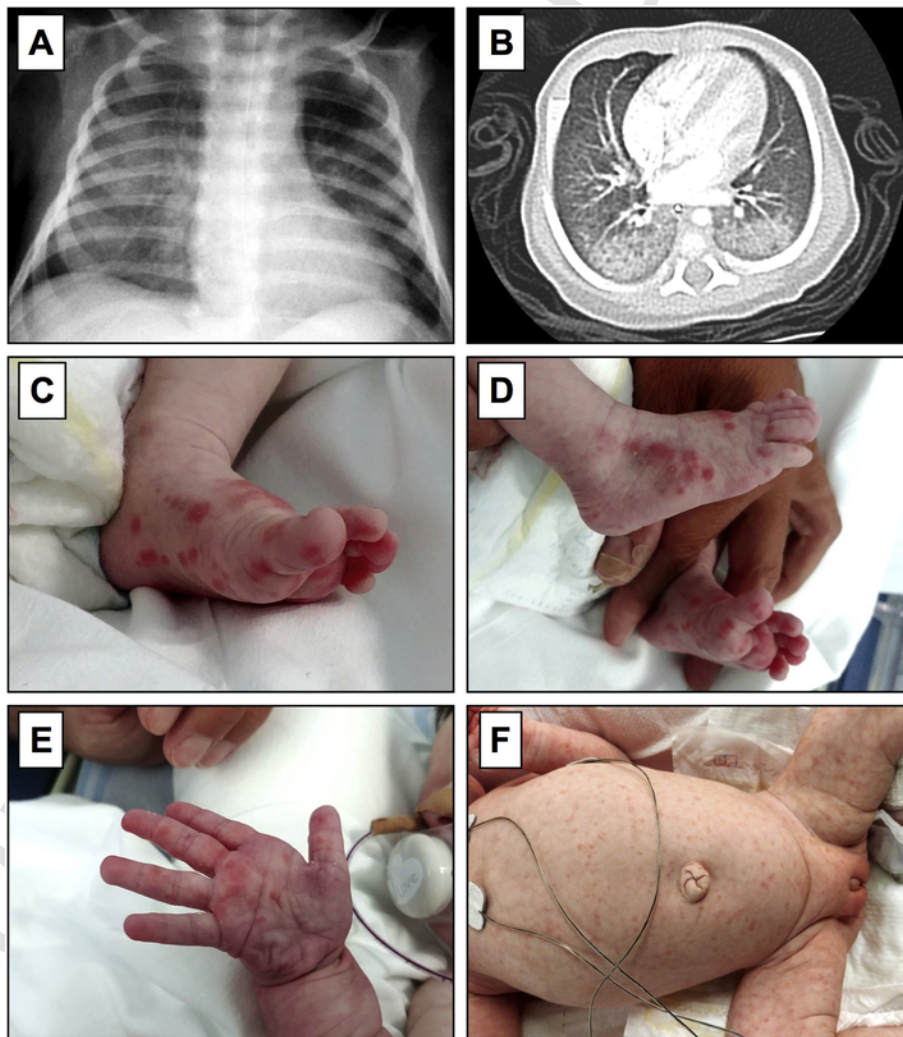


Fig. 1. Chest X-ray (A) and CT scan (B) images of interstitial lung disease. Maculopapular skin rash on extremities (C,D,E) and a different one on the whole body (F).

that point any neonatal infection seemed unlikely, so antibiotics were discontinued. A pediatric hematologist-oncologist was consulted and diagnostic workup for familial haemophagocytic lymphohistiocytosis, neonatal leukaemia and other malignancies was performed. Analysis of bone marrow revealed normal tissue organization and cell morphology, while levels of perforins, neuron-specific enolase and urinary catabolites of catecholamines were also normal. A total body magnetic resonance imaging (MRI) revealed no abnormal mass or bone densities, but showed a mild cerebellar hypoplasia and confirmed the interstitial lung disease. During the following ten days, systemic inflammation persisted and worsened (Fig. 2A), with relapsing episodes of fever (Fig. 2B) and skin rashes of varied appearance (Fig. 1F). The patient required two transfusions of packed red cells for anemia, remained hypotonic and failure to thrive became evident (Fig. 2B). A pediatric rheumatologist was involved in the management of the baby on DOL 24. Systemic inflammation, skin rashes and interstitial lung disease were consistent with a clinical suspicion of SAVI, thus the patient was tested for type-I interferon (IFN) functional signature. In the meanwhile, considering the consanguinity of the parents and the high phenotypic variability of AIDs, a next-generation sequencing (NGS) panel for 41 different AID-related genes was requested, as well as urinary quantification of mevalonic acid and lysine. On DOL 36, type-I IFN signature came back normal, but extremely high levels of mevalonic acid were found in the urine (7024 mM/M of creatinine, normal value < 0.1); lysinuria was within normal levels. NGS confirmed a homozygous c.709A > T missense mutation in the exon 8 of the *MVK* gene, coding for a protein substitution p.T237S, consistent with the diagnosis of MKD. Both parents and the sister were found to be heterozygous carriers of the same mutation.

On DOL 38, after obtaining parental informed consent, treatment with the IL-1 receptor antagonist anakinra was started at the dose of 3.5 mg/kg per dose once daily: the treatment was quickly effective on systemic inflammation, leading to a regression of fever and skin rash, a sharp drop in CRP from 14.4 to 1 mg/dL, an increase in reticulocytes within 48 h and a significant weight gain during the following days (Fig. 2A-B). Hypotonia significantly improved. The patient was discharged from hospital on DOL 56 in good clinical conditions, with CRP within the normal range, on anakinra therapy. Subsequent dose adjust-

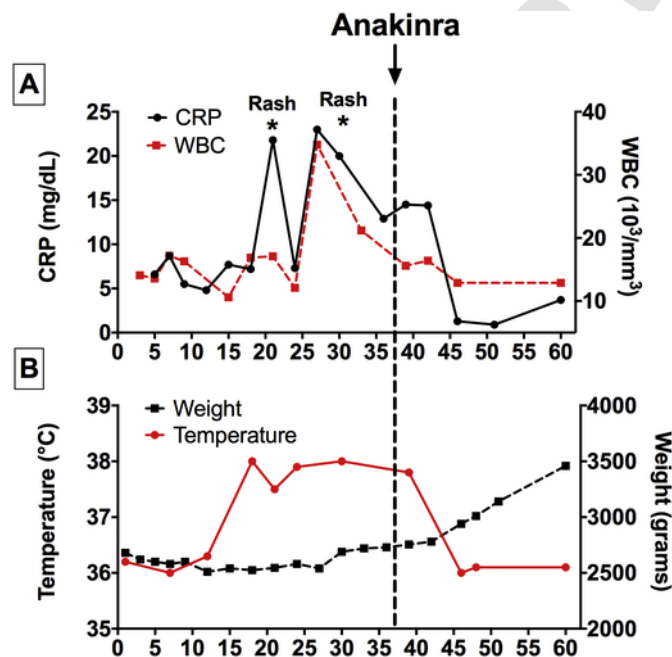


Fig. 2. Laboratory values (A), body temperature and body weight (B) before and after treatment with anakinra.

ment of the drug, up to 4.5 mg/Kg per day, was required to fully control the clinical picture. She is now six months-old, still on anti-IL-1 treatment without adverse events, and with satisfactory control of inflammatory manifestations. Due to severe presentation of the disease and severe enzymatic defect, she is currently undergoing a complete evaluation for future hematopoietic stem cell transplantation (HSCT).

### 3. Discussion

We report here a neonatal-onset case of MKD due to a rare homozygous mutation (p.T237S), mimicking a neonatal infection and with a phenotype characterized by a previously unreported interstitial lung disease.

AIDs are a heterogeneous group of rare diseases caused by an altered regulation of inflammatory responses [5]. Since the first AID, familial Mediterranean fever, was characterized at a molecular level back in 1997 [6], new syndromes and genetic mutations are continuously added to the list of AIDs, and the knowledge of their pathogenetic mechanisms is constantly increasing [7]. AIDs are monogenic diseases, but the involved gene may harbor hundreds of mutations that frequently result in a spectrum of clinical pictures rather than a single, pathognomonic phenotype. This is the case for *MVK* gene, located on chromosome 12q24 and encoding for MVK, an integral enzyme involved in cholesterol and nonsterol isoprenoid biosynthesis.

Mutations in the *MVK* gene are responsible for MKD, with two primary manifestations: mevalonic aciduria (MA-OMIM 610377), the most severe phenotype of MKD, and the hyper-IgD syndrome (HIDS-OMIM 260920) [8]. Clinical severity of MKD has been related to the residual enzyme activity, with MA typically associated with less than 1%. Recurrent episodes of inflammation are the cornerstone of both conditions, with fever, skin rash, diarrhea, vomiting and arthralgia/arthritis associated to increased acute phase reactants, leukocytosis and anemia. Additional features of MA may include failure to thrive, severe neurological impairment, dysmorphic features, cataracts, retinopathy, ataxia, hepatosplenomegaly, and cholestasis. Furthermore, patients with overlapping features, intermediate phenotype or unusual manifestations are not uncommon [9].

MKD affects approximately 300 people worldwide, with 215 mutations in the *MVK* gene described, 51 of which certainly pathogenic. HIDS phenotype is ten times more common than MA [10–12]. MKD with pure HIDS phenotype has an average age at diagnosis of 9.9 years [13], while in a case series of 114 European patients with both HIDS and MA phenotype the median age at onset was 6 months and the median age at diagnosis was 6.5 years [11]. Of note, the diagnostic delay has been dramatically reduced in the past 15 years due to the increased awareness of the disease and to the growing use of new technology in genetic assays.

The diagnosis of MKD in neonates, as of most AIDs, is challenging due to the rarity and unspecific symptoms that frequently recall those of neonatal infections or of other neonatal diseases, such as malignancies. In 2010, Lionetti et al. reviewed the AIDs that could act as a mimickers of neonatal infections and highlighted the importance of an early recognition, because most of them can have devastating permanent consequences if left undiagnosed but, at the same time, may significantly respond to non-specific (i.e. steroids) or targeted (i.e. biological treatment) anti-inflammatory therapy [14].

The neonate here described, initially investigated and treated as a probably infected newborn, was affected by MKD with some peculiar characteristics, namely the very early disease onset, the rare causative mutation, the previously unreported interstitial lung involvement, and the good response to anti IL-1 treatment as an effective bridge treatment to HSCT.

The T237S mutation of our patient has been recently classified as pathogenic by a panel of experts [12], and has been reported in just 4

patients worldwide, 3 homozygous [15–17] and 1 compound heterozygous [11]. In all of them, the described clinical features are consistent with MA phenotype, due to an extremely low or absent residual activity of MVK. The age at onset was known for 2 patients, one of which had perinatal manifestations. Thus, this is the second known case of perinatal onset of MKD due to a homozygous p.T237S mutation. Furthermore, to our knowledge, this is the first case of MKD presenting within the first month of life with interstitial lung disease. Interestingly, a compound heterozygous patient (T237S variant combined with I268T) reported by ter Haar et al. [11] and also included in the case series by Papa et al. [16], manifested recurrent episodes of pneumonia and died because of acute respiratory distress syndrome. No interstitial lung involvement is clearly reported, as well as no lung involvement at all is reported for any of the homozygous patients.

In our case, the interstitial lung disease was confirmed by two different imaging studies, CT and MRI, performed between 20 and 35 DOL, but was presumably already present in the first chest X-ray performed at DOL 5. Interstitial lung disease in neonates has an unclear prevalence, being mainly caused by primary pulmonary anatomic or functional defects, such as acinar dysplasia, bronchopulmonary dysplasia or mutations affecting the synthesis of surfactant proteins [18]. Lung biopsy was not performed in our patient because the diagnosis was made when she was still in acceptable general conditions, and therapy was started before a possible worsening of respiratory function.

The association of early onset systemic inflammation, maculopapular skin rash and interstitial lung disease might be also suggestive for SAVI [19]. All patients with SAVI reported by Liu et al. presented within 8 weeks of life with systemic inflammation, 4/6 had skin rash at disease onset and 5/6 had a confirmed interstitial lung involvement, making the suspicion of SAVI in our patient reasonable. Nonetheless, the negative signature testing for type-1 IFN-stimulated genes and the autosomal dominant inheritance were not consistent with our case. SAVI was finally excluded with genetic testing. This case highlights how symptoms may overlap also among different AIDs, especially at onset, and require a full diagnostic workup including genetic testing for a definitive diagnosis.

As for the treatment, many AIDs have undergone a tremendous improvement in symptoms and prognosis over the past 15 years with the development of targeted (biological) therapies [20]. In MA-HIDS, biological treatment with inhibitors of the IL-1 signaling pathway can be highly effective on systemic inflammation, leading to a prompt improvement in clinical condition, with a crucial steroid-sparing effect [21]. However, anti-IL-1 therapy does not seem to significantly affect the neurological symptoms, probably determined by the disruption in cholesterol synthesis [22]. Three cases of allogeneic bone marrow transplantation and one of HSCT from cord blood stem cells have been reported so far [23,24].

In summary, here we report a case of a neonatal-onset MKD characterized by severe systemic inflammation and atypical interstitial lung disease, initially mistaken for a perinatal infection. The uncommon presentation with interstitial lung disease tangled the differential diagnosis also among AIDs, confirming the frequent phenotypic overlap. Although rare, neonatologists should be aware of AIDs, whose outcome can be dramatically modified by an early diagnosis and adequate treatment. A multidisciplinary approach involving a pediatric rheumatologist in the management of unresolved neonatal systemic inflammation may speed up the correct diagnosis of an early-onset AID and facilitate a prompt start of the appropriate specific therapy.

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## Declaration of interest

None.

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