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Infantile Systemic Inflammatory Disease Associated with a De Novo POMP Intragenic Deletion

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Abbreviations:

SLE: Systemic Lupus Erythematous; SLICC: Systemic Lupus International Collaborating Clinics; ACR: American College of Rheumatology; jSLE: Juvenile Systemic Lupus Erythematous; iSLE: Infantile Systemic Lupus Erythematous; IFN: Interferon; PRAID: POMP-releated autoinflammation and immune dysregulation; DNAse: Deoxyribonuclease; USP18: Ubiquitin Specific Peptidase 18; PRAAS: Proteasome Associated Autoinflammatory Syndrome

1. Abstract

Proteasome maturation protein (POMP), encoded by POMP, is a protein that functions as a chaperone for proteosome maturation. Pathogenic variants in POMP, are associated with the Proteasome-Associated-Autoinflammatory Syndrome (PRAAS), Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome, POMP-related autoinflammation and immune dysregulation disease (PRAID), and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE). We present the case of a 1-month-old girl with an infantile systemic inflammatory phenotype associated with a De Novo intragenic deletion in POMP. Clinical SLE diagnosis was suspected on SLICC and ACR criteria.

2. Introduction

Proteasome maturation protein (POMP), encoded by POMP, is a protein that functions as a chaperone for proteosome maturation. The proteasome is a multisubunit enzyme complex that plays a central role in the regulation of proteins. The incorrect function is now associated with multiple immune dysregulation syndromes [1]. The ubiquitin-proteasome pathway defects have been related with lupus pathogenesis. Juvenile onset systemic lupus erythematous represents around 20% of all SLE cases.2 The exact pathophysiology of jSLE is still unclear, but interferon pathway it's a permanent signature's disease. The age at which symptoms begin, is a crucial factor in the patient's prognosis, and debut before the age of 5 years is very rare [3]. Patients with this disease present with fever, arthralgia, headaches, and weight loss amongst other symptoms. Organ damage is also common, particularly at kidney level, with lupus nephritis affecting around 80% of this group [4]. Monogenic lupus represents a group of genetic mutations that clinical expression looks like systemic lupus erythematous. Some pathways that can cause the development of the disease are interferon pathway dysregulation, and genetic mutations that can affect the development of B or T cells [5].

The gene POMP, located in chromosome 13q12.3, codifies for a chaperone that participates in the proteasome assembly and maturation processes. Haploinsufficiency causing POMP variants produce a proteasome precursors accumulation and a reduction in overall proteasome activity [6]. This defect has been associated with Proteasome-Associated-Autoinflammatory Syndromes.

Herein we present a patient with De Novo POMP Intragenic Deletion with a clinical spectrum suggestive of SLE, characterized

by nephrotic syndrome, hepatic disease, serositis, neurological involvement, thrombocytopenia, and hemolytic anemia during her first year of life.

3. Case Report

Informed consent was obtained from the patient for whom identifying information is included.

We report a 1-month-old female with a history of increased abdominal circumference, jaundice, hypocholic stools, vomiting and seizures since birth. Physical examination revealed microcephaly, jaundice, and hepatomegaly, with laboratory work-up consistent with cholestasis. Anatomical, metabolic, and infectious causes of cholestasis were ruled out (Table 1, Table 2).

During hospitalization, the patient required mechanical ventilation, inotropic and vasopressor support due to ventilatory and hemodynamic instability. Nephrotic syndrome, hematological problems (hemolytic anemia, leukocytosis and thrombocytopenia), and pleural effusion causing serositis were documented at this point.

Complete workout from a multidisciplinary team including gastroenterology, hematology, infectiology, nephrology and rheumatology was performed. Liver biopsy reported a giant cell transformation hepatitis with moderate canalicular cholestasis. A salivary glands biopsy performed to rule out lysosomal storage disorders and Sjögren disease was reported within normal parameters.

Further laboratory results ruled out aminoacidopathies and lysosomal storage disorders. Isolated positive antinuclear antibodies were detected, with other auto-antibodies titers within normal limits (Table 2).

The patient was diagnosed with systemic lupus erythematosus through ACR 1997 criteria (nephrotic syndrome, serositis, neurological involvement, thrombocytopenia, coombs positive hemolytic anemia and positive antinuclear antibodies). SLICC 2012 criteria and EULAR/ACR 2019 (positive ANAs, fever, hematologic disorder, neuropsychiatric disease, serosal, and proteinuria) were also met.

Table 1: Infectious Approach

INVESTIGATIONS	RESULTS	REFERENCE VALUE
Anti-toxoplasma IgG Antibodies	Negative	Negative
Anti-toxoplasma IgM Antibodies	Negative	Negative
Anti-CMV IgG Antibodies	Negative	Negative
Anti-CMV IgM Antibodies	Negative	Negative
Anti-Rubella IgG Antibodies	Negative	Negative
Anti-Rubella IgM Antibodies	Negative	Negative
Anti-Herpes 1 IgG Antibodies	Reactive	No reactive
Anti-Herpes 2 igM Antibodies	Negative	Negative
Surface antigen hepatitis b	Negative	Negative
Hepatitis A total Antibodies	>60 +positive	Negative
Hepatitis A IgM Antibodies	Negative	Negative
HIV-1, HIV-2 Antigens	Negative	Negative
VDRL test	Negative	Negative
Anti-Parvovirus B-19 IgG Antibodies	Negative	Negative
Anti-Parvovirus B-19 IgM Antibodies	Negative	Negative
Anti-Leptospire IgM Antibodies	Negative	Negative

Table 2: Immunological Approach

INVESTIGATIONS	RESULTS	REFERENCE VALUE
Beta 2 glicoprotein-1 IgG Antibody	Negative	Negative
Anti-cardiolipin IgG Antibody	Negative	Negative
Anti-cardiolipin IgM Antibody	Negative	Negative
Anti-MPO Antibody	Negative	Negative
Anti-PR3 Antibody	Negative	Negative
Lupus anticoagulant	Negative	Negative
Anti-nuclear Antibodies	Homogeneous 1.160	Negative
Anti-Ro / La Antibodies	Negative	Negative
Anti-dsDNA Antibodies	Negative	Negative
Anti-Smith Antibody	Negative	Negative
Anti-LKM Antibody	Negative	Negative
Anti-SMA	Negative	Negative

Abbreviations: IgG, immunoglobulin G. IgM, immunoglobulin M. MPO, Myeloperoxidase. PR 3, Proteinase-3. dsDNA, Double-stranded DNA. LKM, Liver/Kidney Microsome. SMA, smoth muscle antibody, Citomegalovirus, Venereal Disease Research Laboratory

Taking into consideration that monogenic SLE diagnosis include ruling out all pathologies, including immunodeficiencies. A 156 genes panel for Autoinflammatory and Autoimmunity Syndromes Panel that includes complement related disorders, B and T-cell pathways and interferonopathies was performed at an external clinical laboratory (Invitae Corp ©) through next generation sequencing. Prior informed consent from the patient's parents, genomic DNA was obtained from a whole blood sample collected on an EDTA tube. Enrichment for targeted regions and sequencing with a ≥50x depth was performed using Illumina technology. A previously unreported intragenic Exon 6 deletion at POMP (NM_015932.5) was reported. This finding was initially classified as a Variant of Unknown Significance, but it was reclassified as Likely Pathogenic using the 2015 ACMG criteria after performing a segregation analysis which showed a de novo mutation.

An intravenous immunoglobulin and methylprednisolone combined regimen was initiated. Significant clinical improvement was observed after initial treatment, resulting in the cessation of inotropic and ventilatory support. Maintenance treatment with prednisone, mycophenolate mofetil and cyclosporine was initiated. The patient persisted with leukocytosis but without thrombocytopenia, anemia, or neurological impairment. Proteinuria gradually diminished until reaching a negative status. Jak inhibitors could not be obtained for this patient for economic reasons. After 6 months of treatment pharmacologic remission was documented. During the steroid reduction scheme, proteinuria, anemia, and leukocytosis were observed again at laboratory controls. Intravenous immunoglobulin infusion and methylprednisolone were reinitiated due to a severe disease flare characterized for a catastrophic brain hemorrhage, renal failure, autoimmune hemolytic anemia, thrombocytopenia, and leukocytosis. A not-previously observed chickenpox-like rash was observed in the patient, for this reason a skin biopsy and a bone marrow aspirate were obtained reported with skin predominant neutrophilic inflammatory infiltrate, with no vasculitis, and no malignant cells at bone marrow. Despite our best efforts, and after another regimen of IVIG and steroids the patient had a fatal outcome and died. After she died, we considered other diagnosis like PRAAS or PRAID, however, no more studies were realized.

4. Discussion

Systemic lupus erythematous is a multisystemic auto-immune disease. The exact pathophysiology of jSLE is still unclear. Early-onset cases of SLE are characterized of being more aggressive, the clinical features include lose weight, fever, and around 80% of the patients develop lupus nephritis [4].

Our patient doesn't reveal relevant family history, also has not familiar history of immune diseases, either consanguinity. This is relevant for monogenic lupus, making less probable this diagnosis. However, our patient satisfies SLICC7 criteria (serositis, renal, neurologic, hemolytic anemia, thrombocytopenia, ANA and positive direct coomb's test), and ACR8 criteria (Neurologic disorder, renal disorder, serositis, hematologic disorder and ANA) for SLE, and we did not have any other cause to the patient symptoms and evolution, the genetic testing revealed a mutation in the POMP. The immune dysregulation at Ubiquitin-Proteosoma system has been related with an interferon pathway up-regulation, under mechanism poor understood. And IFN is the "classic lupus cytokine". By the other hand our patient presents with positive antinuclear antibodies, but other negative immune markers of SLE, inclusive conserve adequate complement levels, suggesting another differential etiology mimicking SLE.

The genetic evaluation was performed to the parent's patient as well, and the result was negative for the gene POMP mutation, with this information and with the absence of familiar history of autoimmune diseases, we can consider the mutation as, novo one.

There are just some case reports like our patient. The clinical features were very common between the previous case reports and our case (Renal, hematologic and neurological features). But there are not genetic studies in all cases.

The proteasome way has been associated mainly with autoinflammatory syndromes. Notable advances in gene sequencing methods in recent years have permitted enormous progress in the phenotypic and genotypic characterization of autoinflammatory syndromes. Some peculiar clinical features may lead to susception, including an early necrotizing vasculitis, or an early systemic lupus erythematous (SLE). In this way it's important to consider Type I interferonopathies, by the interferon common pathway in the pathophysiology in these group of diseases. Monogenic lupus disease was first described in patients with gene mutations at interferon signaling pathway [15]. Some of the clinical characteristic in these disorders are early onset of neurological involvement, livedo reticularis, skin vasculopathy, chilblain lesions, panniculitis or renal disease. In our case when we consider differential diagnosis, we didn't have on mind a specific mutation, and because of the limited literature was not very useful. The lupus early onset cases, have not genetic test commonly reported.

The adequate proteasome system function is necessary for cellular proteostasis, controlling protein synthesis, folding, trafficking and clearance machineries. The perturbation at some point could take the pathway to autoinflammation, with common feature of interferon over-production and chronic inflammation under pathogen-free conditions. The ubiquitin system belongs to proteasome structure, and its play a crucial role in cell cycle regulation, antigen presentation, regulation of gene expression, differentiation and many other, including no-proteasome ways. The ubiquitin cascade activation direct substrate to catalytic complex of proteasome [16,17]. The POMP (Proteasome maturation protein) participates like a chaperone to the proteasome assembly, specifically in the middle of the ring, helping to the β-subunits. POMOP mediates the association of pre20S with the endoplasmic reticulum, recruits the remaining β-subunits into the nascent complex and supports the final proteasome maturation [18]. However, this proteasome looks like standard proteasome, and under stress conditions, could change to "immunoproteasome", for example during immune responses, making a conformational change in core particle or regulatory particle. At both POMP works like chaperone [19, 20].

The proteasomal dysfunction may lead to increased IFN signaling through a mechanism being defined. PRAID (POMP-related autoinflammation and immune dysregulation) was described by Cecilia Poli, et al, which was considered an interferonopathy with autoimmune or autoinflammatory phenotypes [21]. They suggest an association between POMP variants and increased IFN Signature, predominant by negative mechanism. However, the step-to-step pathogenic way it has not demarcated. Two cases previously reported a heterozygous POMP variant. (Figure 1) Consistent with our case. Although those prior reports did not evaluate biological mechanism by which variation in POMP contributes to disease, like our situation [19, 22]. It is interesting that the patient had a heterozygous mutation of POMP gene. The genetic evaluation was performed to the parent's patient as well, and the result was negative for the gene POMP mutation, with the absence of familiar history of autoimmune diseases, and in absence of consanguinity we can consider the mutation as novo one. Considering the delicate ubiquitin system, any simple modifications could be relevant, as we can see at Joint contractures, Muscle atrophy, Microcytic anemia, and Panniculitis-induced childhood-onset lipodystrophy (JMP) syndrome, Nakajo-Nishimura syndrome (NNS) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) where an autosomal recessive homozygous or compound heterozygous loss-of-function mutations cause the early presentation of all these diseases [23]. The Candle syndrome it's the representative disease at this point. By the way the gene POMP has been describe in association with PRAAS (Proteasome Associated Autoinflammatory Syndrome), an autosomal related disease that include the Candle Syndrome too. Our patient presents a Gene POMP variant, however, doesn't have panniculitis with lipodystrophy, splenomegaly, or brain calcifications, so we don't consider a Candle Syndrome like predominant phenotype. But is relevant that the skin biopsy at the moment of dead reported a neutrophilic dermatosis, so, the Candle Syndrome and our case have again some similarities.

The Aicardi-Goutiere Syndrome is a progressive encephalopathy associated with interferon pathway, characterized by progressive decline in head growth, liver abnormalities in the early onset form, epileptic seizures, thrombocytopenia, hepatomegaly and hemolytic anemia, a common clinical phenotype with the case report here. Some authors mention that these diseases could be a variant of monogenic lupus24. Our patient has not the Aicardi-Goutiere Syndrome phenotype (Figure 1), and there is no relation with nephrotic syndrome, serositis and the treatment response with cyclosporine, mycophenolate mofetil or steroids.

PRAAS are a heterogenous group of interferonopathies caused by mutations in genes encoding proteasome subunits (PSMB8, PSMB9, PSMA3) or chaperone factors such as POMP [15, 25]. The proteasome pathway is necessary for normal protein clearance working together with ubiquitin system. The failure at this system is associated with activation of the IFN pathway, in a molecular not fully understood way. Some clinical features are pernio-like purplish nodular lesions, panniculitis, lipodystrophy, joint contractures, neurologic disease, and microcephaly. Again, some common clinical features were described in our case. PRAID has called a PRAAS 2 syndrome. PRAID is an immune dysregulation syndrome characterized by autoimmunity, immunodeficiency, and inflammatory disease. The immunological defect is a dominant-negative mechanism. Demonstrated by Poli et al, only in truncating

variants in POMP. Defining PRAID like an inherent immunological defect mechanistically characterized by NMD (nonsense-mediated mRNA decay) escape. It's interesting the association of PRAID with $CD4^+$ / $CD8^+$ T cells ratios in both individuals described by Poli et al. At our case the $CD4^+$ / $CD8^+$ T cells ratios was elevated (5.64) like PRAID syndrome with predominantly naive T cells. But our patient doesn't have an immunodeficiency evident syndrome. With no infectious complicated course or opportunist infectious agent isolations at any human compartment. Other relevant case information was the persistent leukocytosis since debut to dead. Getting leukocyte count at high as 50,430µl, with neutrophil predominance, suggesting an inflammatory immune response. Inclusive in absence of infectious agent [21].

In summary, our patient debut with a variety of clinical and serological features, some of this could associated with POMP related diseases, like CANDLE, PRAAS or PRAID syndrome. But others could be related with direct interferonopathies like Aicardi-Syndrome. All of this could be match by POMP defects, and our patients has a De Novo POMP Intragenic Deletion, so we speculate the inflammatory phenotype at our case in relation with a POMP defect.

The approach to this patients' needs an interdisciplinary work team. In case of suspicion, IFN signaling, and proteasome pathway should always be evaluated. The IFN signature it's not accessible in all the world, for this reason the genetic approach with exome or whole-genome sequencing looks like better option in these circumstances. One of our limitations was the absence of cellular mechanism evaluation, making the POMP association hard to demonstrate. The POMP pathogenic way looks like other way to walk at science.

The treatment options at this point are no specific, impacting the prognosis and organ damage, some options include intravenous methylprednisolone or immunoglobulins, mainly in acute phase. However, are not always resolutive. Posterior could be necessary treatment with JAK inhibitors, or monoclonal antibodies targeting IFN or resulting in indirect negative gain IFN production. The hematopoietic stem cell transplantation looks like an option; however, we need more studies supporting this therapy. The actual prognosis is not clear.

We are aware of the limitations at relation with the genetic studies, and the necessity of Multiplex ligation-dependent probe amplification (MLPA) to verify the exon variation. However, the MLPA is

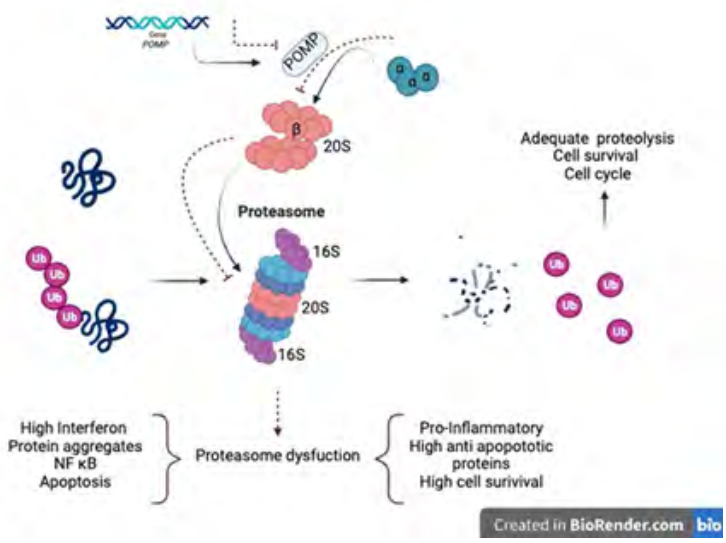

Figure 1: The normal proteasome function leads to adequate proteolysis, cellular survival, and cellular cycle. Defects on Gene Pomp or their chaperone protein POMP leads to proteasome dysfunction with consequent high interferon levels, protein aggregates, high NF κB activation, apoptosis, pro-inflammatory response, high anti apoptotic proteins and high cell survival. NF κB: Nuclear factor kappa B, Ub: Ubiquitin.

5. Conclusion

We report the case of pediatric inflammatory disease, with suspicion of SLE. We propose that every patient with an unexplained multisystemic disease, an immunologic investigation and genetic evaluation for SLE and other autoimmune and autoinflammatory diseases should be considered, especially with the early onset patients. Monogenic SLE is very hard to associate with POMP deletion at our patient, however, we suggest an anormal proteasome function associated with this POMP deletion and a possible anormal IFN pathway like the cause of the clinical and serological curse at the actually case report. Unfortunately, functional studies could not be performed in our patient due to lack of resources and her early demise. More studies are necessary to corroborate the relation of POMP with other pathologies like SLE.

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