LETTER TO EDITOR

PAMI Syndrome: Two Cases of an Autoinflammatory Disease with an ALPS-Like Phenotype

Fionnuala Cox1 · Venetia Bigley2 · Alan Irvine3 · Ronan Leahy4 · Niall Conlon1

Received: 9 January 2022 / Accepted: 24 March 2022 / Published online: 19 April 2022
© The Author(s) 2022

To the Editor,

Proline-serine-threonine phosphatase interacting protein-1 (PSTPIP1)–associated myeloid-related inflammatory (PAMI) syndrome with hyperzincemia is a rare autoinflammatory disorder associated with enhanced pyrin activity and inflammasome activation. Clinical features include cutaneous and systemic inflammation, failure to thrive, hepatosplenomegaly, lymphadenopathy, and cytopenias. Pathogenic variants in

\[ \text{PSTPIP1} \]

are frequently associated with pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome [1, 2]. Patients with PAMI have distinct mutations (E250K or less commonly E275K), and exhibit more pronounced systemic inflammation and cytopenias but less joint involvement than individuals with PAPA syndrome [3].

We present two unrelated, Caucasian Irish cases of PAMI syndrome and describe the inflammatory signature associated with the condition. Both patients have the same heterozygous E250K variant in

\[ \text{PSTPIP1} \]

; one was diagnosed as an adult, the other in childhood.

Patient 1

The first patient is a 46-year-old Irish male born to non-consanguineous parents with no family history of note. At 2 years, he developed colitis, failure to thrive, recurrent lower respiratory tract infections, and juvenile idiopathic arthritis (JIA). He was noted to have selective IgA deficiency, with a polyclonal elevated IgG. In adolescence, he developed neutropenia and thrombocytopenia refractory to steroids and ultimately had a splenectomy. Post splenectomy, the platelet count recovered; however, neutropenia persisted. Early adulthood was characterized by non-malignant lymphadenopathy, intermittent synovitis, and nodulo-cystic acne. There were occasional flares of colitis and minor respiratory tract infections. A lymph node biopsy was consistent with reactive changes, follicular hyperplasia, and preserved architecture, while bone marrow aspirate demonstrated a hypercellular marrow. Inflammatory markers were persistently elevated (Table 1). The patient was reviewed at two international centers of excellence during early adulthood in search of clarity on a diagnosis. Next-generation sequencing (NGS, “TIGER Panel”) available at the time was uninformative. In light of clinical feature, an elevated vitamin \( B_{12} \) increased double-negative T cells (DNT) and repeated abnormal apoptosis assays (CD95L induced apoptosis assay of PHA-treated blastocysts; Table 1); a diagnosis of autoimmune lymphoproliferative syndrome (ALPS) was proposed.

Further phenotyping of the DNT population was not typical of ALPS (CD45RA −, CD38 +) and ALPS-associated mutations were not identified by targeted testing. At 44 years of age, a more comprehensive NGS panel for primary immunodeficiency and autoinflammatory conditions (“Invitae”) identified a heterozygous pathogenic variant (E250K) in the

\[ \text{PSTPIP1} \]

gene. Plasma IL-1β was grossly elevated in the absence of infection, while levels of IL-6, TNFα, IFNγ, and IL-8 did not differ from controls. Levels of the inflammasome scaffold protein ASC (apoptosis-associated speck-like...
protein containing a carboxyterminal CARD) were also elevated suggesting activation of the pyrin inflammasome. Subsequent assessment revealed a marked elevation of serum zinc at 192 μmol/L supporting a diagnosis of PAMI syndrome. Treatment with the IL-1β receptor antagonist anakinra was commenced but an initial response was not maintained. The patient was switched to adalimumab resulting in improvement to musculoskeletal symptoms and lowered inflammatory markers. This has not been sustained long term. Currently, there is consideration to discontinue adalimumab and trial the IL-6 receptor blocker tocilizumab.

### Patient 2

A 15-year-old Caucasian Irish male presented at 6 months of age with prominent splenomegaly and severe anemia. Hemoglobin at presentation was 54 g/L and he required multiple red cell transfusions. Neutropenia and thrombocytopenia were also noted. He suffered recurrent respiratory tract infections, diarrhea, and lymphadenopathy. Anemia improved after a course of oral corticosteroids, but neutropenia, lymphadenopathy, and splenomegaly

### Table 1

| Laboratory characteristics | Patient 1 | Patient 2 |
|---------------------------|-----------|-----------|
| **Biochemistry**          |           |           |
| Serum zinc (μmol/L)       | 185       | 88 (9–22) |
| Serum calprotectin (ng/mL)| Not measured | 385 (26–78) |
| LDH (U/L), pre-treatment  | 453 (135–250) | 1389 (325–670) |
| Ferritin (ng/mL), pre-treatment | 340 | 1250–2152 (21–274) |
| CRP (mg/L), pre-treatment | 42–95     | 34–94 (< 5) |
| Serum amyloid A (mg/L), pre-treatment | 22–140 | 6.4–222 (< 5) |
| C3 (g/L)                  | 1.46      | 1.94 (0.7–1.7) |
| C4 (g/L)                  | 0.26      | 0.29 (0.09–0.4) |
| Serum vitamin B₁₂ (pg/mL) | 1277      | 1178 (197–866) |
| Serum Fas ligand           | Normal    | Normal    |
| Apoptosis*                | Abnormal  | Not measured |
| **Serology**              |           |           |
| IgG (g/L)                 | 21.6      | 12 (3–9)  |
| IgA (g/L)                 | <0.05     | 0.96 (0.15–0.7) |
| IgM (g/L)                 | 0.7       | 2.3 (0.4–1.6) |
| Anti-nuclear antibody     | Negative  | Negative  |
| Anti-neutrophil antibody  | Negative  | Negative  |
| Rheumatoid factor         | Negative  | Negative  |
| **Lymphocyte subsets (values in cells/μL)** |           |           |
| T cells (CD3+)            | 1980 (797–2996) | 1568 (700–4200) |
| CD4+ T cells              | 889 (502–1749) | 947 (300–2000) |
| CD8+ T cells              | 757 (263–1137) | 527 (300–1800) |
| TCRαβ+ T cells (%)        | 83        | 89        |
| TCR γδ+ T cells (%)       | 10        | 11        |
| Double-negative T cells (% CD3+ cells) | 7 | Not detected |
| B cells (CD19+)           | 422 (99–618) | 908 (200–1200) |
| **Plasma cytokines (pg/mL)** |           |           |
| IL-1β                     | 407       | 2.6 (0.00–1.26) |
| ASC                       | 146.7     | 17.24 (0–0.2) |
| TNFα                      | 24.3      | 19.5 (0.00–22.59) |
| IL-8                      | 36.7 (0.00–33.01) | Not detected |
| IL-6                      | 37.9      | 40.4 (0.09–7.26) |
| IFNγ                      | 27.2      | Not detected |
Our initial investigations focused on identifying an underlying cause for the constellation of splenomegaly and lymphadenopathy in the context of immunodeficiency and autoimmunity, clinical findings not typical of autoinflammatory disease. In light of clinical presentation, non-contributory early genetic studies, and biomarkers (elevated DNT, polyclonal IgG, raised vitamin B₁₂, impaired apoptosis), a diagnosis of ALPS-U felt reasonable. Continued observation and improved access to genetic testing lead to a diagnosis of PAMI syndrome.

Our observation of increased baseline lymphocyte counts could indicate an impaired apoptotic pathway, or enhanced cell survival, which underlies the characteristic lymphadenopathy and autoimmune phenotype. Case one demonstrated abnormal apoptosis on repeated assessments, again suggestive of ALPS (Table 1). Whole exome analysis of a pediatric cohort with autoimmunity and lymphoproliferation reminiscent of ALPS identified a single case with the E250K variant of PSTPIP1 [4].

The pathogenesis of PAMI syndrome has not been fully elucidated. PSTPIP1 is a cytoskeletal-associated adaptor protein that interacts with pyrin, allowing for the formation and activation of the pyrin inflammasome, which culminates in the caspase-1-dependent processing of inflammatory mediators including IL-1β and IL-18 into their mature form [5]. The oligomerization of the pyrin inflammasome involves an interaction with ASC, a component shared with the NLRP3 inflammasome. It is hypothesized that E250K causes a charge reversal within the PSTPIP1 gene, which increases its proclivity for pyrin, amplifying cytokine release and sequestration of the alarmins MRP-8 and-14 [3]. The elevated levels of ASC identified in both cases are suggestive of baseline activation of the pyrin inflammasome.

Hyperzincemia is pathognomonic for PAMI syndrome, possibly representing a pseudo-elevation, as functional stores are likely depleted due to MRP’s high zinc-binding capacity [5]. Zinc has a key immunomodulatory role in signal transduction and cell-mediated immunity, with deficiency known to result in immune dysfunction. The absence of free-zinc in PAMI syndrome possibly contributes to the associated immunodeficiency profile. There is currently no evidence to use zinc supplementation in these patients.

These cases add from the handful of published case reports to the body of clinical data on PAMI syndrome and illustrate a disease with features of autoinflammation and non-malignant lymphoproliferation. PAMI syndrome should be considered in genetically unidentified cases of ALPS (ALPS-U) or in individuals with incomplete manifestations of the disease. Assessment of serum zinc levels may be a useful and cost-effective preliminary screening test in patients suspected of having this condition. We identified elevated ASC levels in both cases suggesting baseline pyrin activation driving inflammation. Both of our patients
demonstrated an initial response to TNF blockade, improved musculoskeletal symptoms, and lower inflammatory markers. Unfortunately, symptom control is waning in patient one and other therapy is being considered; thus, optimum treatment for PAMI is not clear. The determination of the PSTPIP1 variant ended a 44-year diagnostic odyssey for case one and offered both patients improved therapeutic options and established diagnostic certainty. PAMI syndrome has been diagnosed in acutely unstable neonates, as well as clinically stable adults with indeterminate symptoms, emphasizing the age range at which a definitive diagnosis can be made. As NGS becomes part of routine pediatric and adult care, these cases illustrate the increasing importance of genetic testing and revisiting diagnoses in long-standing patients as new disease entities emerge.

Acknowledgements We thank the patients and their caregivers for permission to share this case report with the scientific community. We acknowledge the clinical teams in St. James’s Hospital and Children’s Health Ireland at Crumlin who are involved with ongoing care. We are grateful for the help of Dr. Sinisa Savic, Leeds Teaching Hospital, for aiding with the investigation of these patients.

Author Contribution FC, AI, RL, and NC wrote the case reports and interpreted data, in addition to diagnosing and managing the patients. All authors contributed to the approval of the manuscript.

Availability of Data and Materials Please contact the corresponding author Dr. Fionnuala Cox at coxff@tcd.ie if you wish to request further information on the data.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Patients provided informed consent for this case report to be published.

Competing Interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Demidowich AP, et al. Genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). Arthritis Rheum. 2012;64(6):2022–7. https://doi.org/10.1002/art.34332.

2. Marzano AV, Borghi A, Meroni PL, Cugno M. Pyoderma gangrenosum and its syndromic forms: evidence for a link with autoinflammation. Br J Dermatol. 2016;175(5):882–91. https://doi.org/10.1111/bjd.14691.

3. Holzinger D, et al. Single amino acid charge switch defines clinically distinct proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)-associated inflammatory diseases. J Allergy Clin Immunol. 2015;136(5):1337–45. https://doi.org/10.1016/j.jaci.2015.04.016.

4. Takagi M et al. (2018) Genetic heterogeneity of uncharacterized childhood autoimmune diseases with lymphoproliferation. Pediatric Blood Cancer 65(2).

5. Shoham NG, et al. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. Proc Natl Acad Sci U S A. 2003;100(23):13501–6. https://doi.org/10.1073/pnas.2135380100.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.