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CPD

Severe ulcerative proctitis, pyoderma gangrenosum, hidradenitis suppurativa and fever in a patient with a rare variant of the *PSTPIP1* gene

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doi: 10.1111/ced.14754

Autoinflammatory syndromes are characterized by unprovoked, persistent inflammation. We describe a 67-year-old man who presented with severe proctitis, pyoderma gangrenosum, hidradenitis suppurativa and fever, and was found to have a rare variant of the *PSTPIP1* gene.

The patient had a history of Type 2 diabetes, hypertension and hypercholesterolaemia and was first investigated due to the presence of microscopic faecal blood at the age of 60 years. Adenomas were excised at this time. Four years later, the patient had an intestinal haemorrhage that led to anaemia. Colonoscopy detected ulcerations in the anal canal. The proctitis was self-limiting, but occasional bleeding prevailed. Three years later, palatal and scrotal ulcers were detected (Fig. 1a). The clinical and histological findings were suggestive of pyoderma gangrenosum (Fig. 2a).

A week later, pustular lesions appeared on the patient's buttocks, hips and shoulders (Fig. 1b), and histological analysis supported the diagnosis of hidradenitis suppurativa (Fig. 2b,c). Faecal calprotectin (FCP) level was 3825 μg/g faeces (positive at levels > 100 μg/g). The patient also had a fever of 38 °C. Colonoscopy revealed severe proctitis with deep ulcers (Fig. 1c). Computed tomography of the colon was normal.

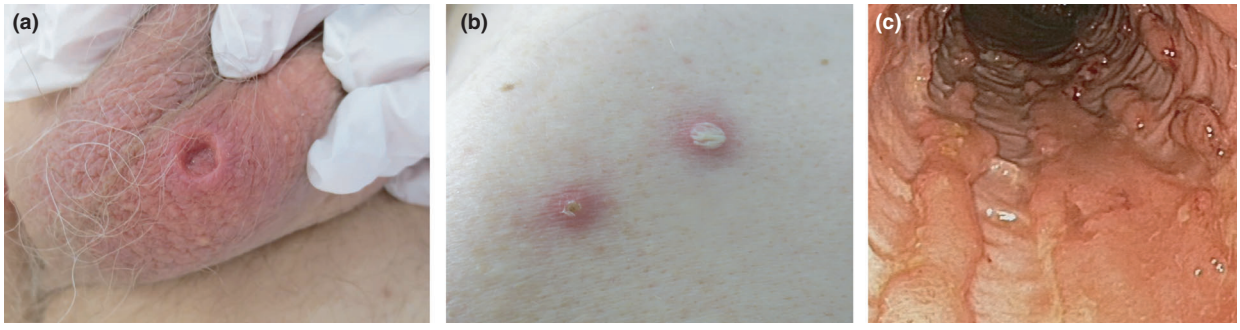

Figure 1 (a) Painful scrotal ulcer measuring 10 mm in size; (b) inflammatory lesions in the shoulder region; (c) endoscopic image of severe proctitis with deep ulcers resembling, but not typical of, Crohn disease.

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Conflict of interest: the authors declare that they have no conflicts of interest.

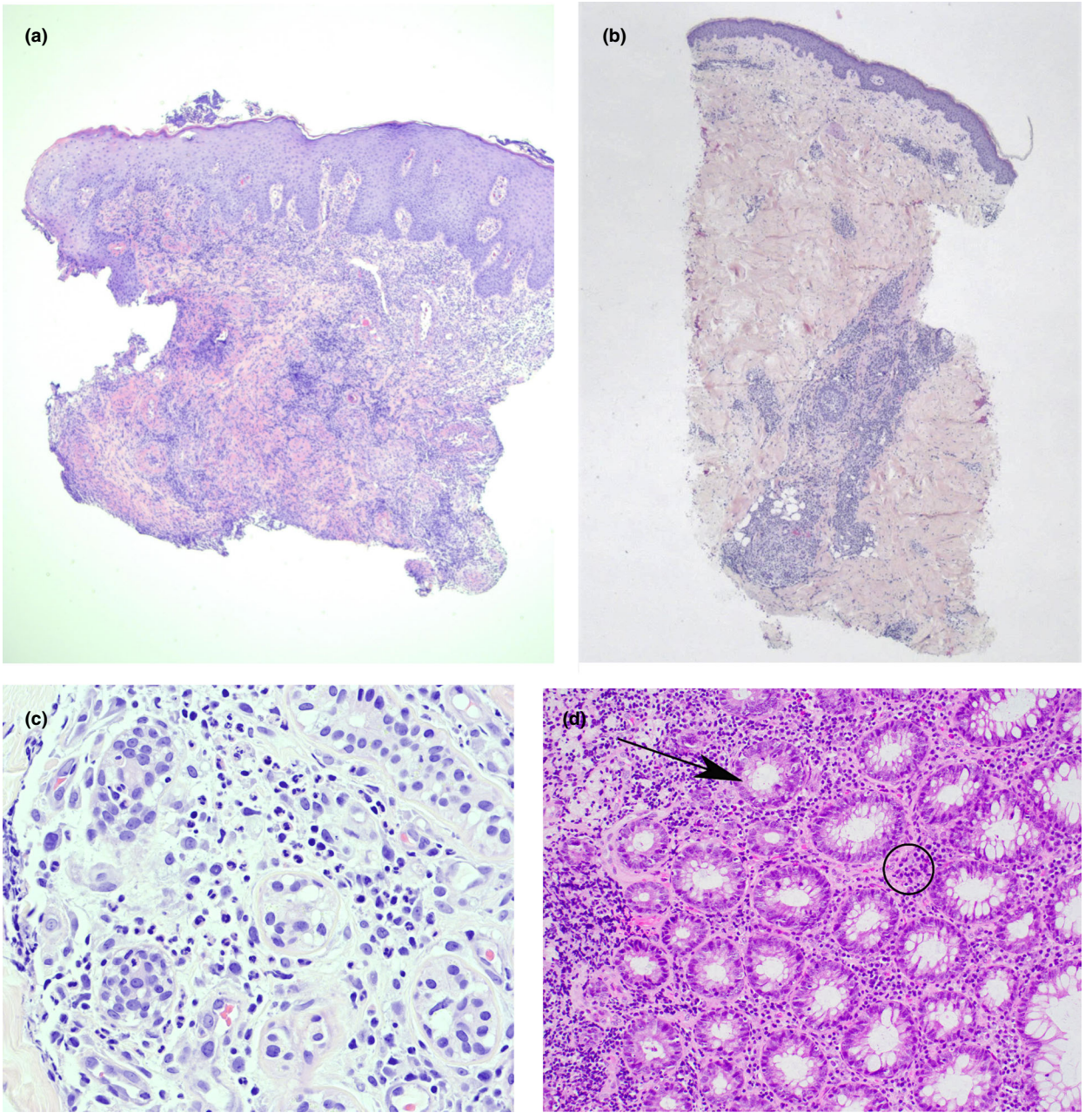

Figure 2 (a) Punch biopsy taken from the edge of a scrotal ulcer, showing dermal inflammation with neutrophils and vascular fibrinoid degeneration without leucocytoclasia. The 'hanging' epidermis at the edge of the ulcer is compatible with, but not diagnostic of, pyoderma gangrenosum. (b) Punch biopsy taken from an inflammatory lesion in the shoulder region revealed dermal, mainly periadnexal and perivascular inflammation. (c) Higher magnification of the same biopsy showing neutrophilic inflammation of the sweat glands. (d) Sample from the severely inflamed rectal mucosa; the crypt architecture was preserved, but the crypt epithelium partially lost its secretory capacity and the nuclear chromatin was reactively coarse (arrow). A dense inflammatory infiltrate composed mainly of lymphocytes is visible in the lamina propria (circle). Haematoxylin–eosin staining, original magnification (a) × 40; (b) × 20; (c) × 400; (d) × 200.

The patient was treated with intravenous methylprednisolone 40 mg and 20 mg (morning and afternoon, respectively) for 5 days, followed by oral prednisolone, which was started at 40 mg and then tapered by 5 mg/week, with weekly subcutaneous injections of methotrexate 25 mg. After 7 weeks of

treatment, the skin symptoms cleared. The intestinal bleeding also ceased, but the diarrhoea continued for several months. Magnetic resonance imaging showed proctitis. Prednisolone was continued at 10 mg/day, but methotrexate was stopped due to lymphopenia. Six months after starting the corticosteroids, sigmoidoscopy showed no inflammation, the FCP level had decreased and the patient was asymptomatic. The patient is currently taking methylprednisolone 5 mg/day and using topical mesalamine.

Following informed consent from the patient, we performed genetic analyses on the patient's DNA extracted from peripheral blood. A targeted panel (Custom Clinical Exome Solution Kit; SOPHiA GENETICS SA, Saint Sulpice, Switzerland) was used for next-generation sequencing (Illumina, San Diego, CA, USA). Autoinflammatory syndrome-related gene sequences, including *NCSTN*, *PSTPIP1*, *MEFV*, *NOD2* and *NOD1*, were screened. The assay provided 50 × coverage of all target regions. Variant annotation and filtering were performed with DDM™ software (SOPHiA GENETICS SA) and visualized by the Integrative Genomics Viewer (https://software.broadinstitute.org/software/igv/). The genetic analysis revealed a rare heterozygous variant [NM_003978.4, c.764C>T, p.(Thr255Met), rs766895096] in *PSTPIP1*. The variant had an allele frequency of 0.0072% in the gnomAD database. The variant was localized to exon 11 and caused substitution of a moderately conserved threonine residue by a methionine at position 255. This substitution was likely to affect the secondary structure of the protein due to differences in the polarity, size and charge present with these residues. The variant had a Combined Annotation Dependent Depletion score of 22.5. The other tested genes were normal.

Several autoinflammatory syndromes are associated with a mutation in *PSTPIP1*, including PAPA (*p*yogenic *s*terile arthritis, *p*yoderma gangrenosum and *a*cne), PASH (*p*yoderma gangrenosum, acne and *s*uppurative *h*idradenitis), PAMI (*P*STPIP1-*a*ssociated *m*yeloid-related-proteinaemia *i*nflammatory), PAPASH (*p*yogenic *a*rthritis, *p*yoderma gangrenosum, *a*cne and *s*uppurative *h*idradenitis), PAPA-like (*p*yogenic *a*rthritis, *p*yoderma gangrenosum and *a*cne-like) and PAC (pyoderma gangrenosum, *a*cne and ulcerating *c*olitis) syndromes.[1–6]

The *PSTPIP1* gene variant detected in our patient was a missense variant, similar to the variant reported in a previous patient with PAC syndrome.[5] Both patients had colitis and pyoderma gangrenosum. However, the patient with PAC syndrome developed symptoms at a younger age than did our patient. In addition, unlike our patient, the patient with PAC syndrome experienced severe acne and did not have clinical improvement with oral prednisolone.

We have found no previous descriptions of proctitis, pyoderma gangrenosum, hidradenitis suppurativa and fever occurring in the presence of a *PSTPIP1* variant. Therefore, we suggest that this should be called PPHSF syndrome and should be added to the increasing number of PSTPIP1-related autoinflammatory diseases.[6]

References

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CPD questions

Learning objective

To gain up-to-date knowledge on autoinflammatory syndromes related to the *PSTPIP1 gene*.

Question 1

What type of symptoms are common to all *PSTPIP1*-related autoinflammatory diseases (PAIDs)?

(a) Dermal.
(b) Neurological.

(c) Ophthalmological.
(d) Pulmonary.
(e) Urological.

Question 2

What is the only *PSTPIP1*-related syndrome previously described to include gastroenterological symptoms?

(a) PAC.
(b) PAMI.
(c) PAPA.
(d) PAPA-like.
(e) PAPASH.

Instructions for answering questions

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- Reflect on the article.
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions.
- Complete the required evaluation component of the activity.

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

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