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LETTER TO THE EDITOR

Successful use of adalimumab to treat pyoderma gangrenosum, acne and suppurative hidradenitis (PASH syndrome) following colectomy in ulcerative colitis

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Dear editor,

PASH syndrome is a recently reported rare condition that consists of a triad of pyoderma gangrenosum, acne and suppurative hidradenitis. It is described as an auto-inflammatory disorder, similar to PAPA syndrome (pyoderma, acne and pyogenic arthritis) but without joint involvement, satisfying the criteria of a disease entity distinct from infection, allergy and autoimmune disorders. A specific underlying genetic mutation for PASH has not yet been identified. Literature on the condition is limited with only two cases reported in our PubMed and MEDLINE searches. We present, to our knowledge, the first documented case of PASH following colectomy for ulcerative colitis and our experience of its management with the anti-TNF therapy adalimumab.

A 26-year-old female presented with 6 weeks of multiple painful discharging open wounds in her axillae and groin. She was noted to have a large acneiform cyst on her right jaw line. Her past medical history included suppurative hidradenitis diagnosed 4 years previously managed with erythromycin, facial cystic acne with significant depressed scarring for which she took Dianette, ulcerative colitis refractory to steroids and infliximab requiring subtotal colectomy with ileostomy and rectal stump formation 18 months prior. She had no joint symptoms and no recent bowel symptoms and was a non-smoker. There was no known family history of dermatological or bowel disorders.

Laboratory investigations revealed normal renal function, erythrocyte sedimentation rate, rheumatoid factor, complement, immunoglobulins and electrophoresis with negative coeliac and hepatitis serology. Autoimmune screen was negative except for a raised p-ANCA of 40 units/ml, and white cell count and C-reactive protein were elevated when her skin condition flared. Normal villi were seen on duodenal biopsies. Swabs cultured *Staphylococcus aureus* in her axillae and bacteroides from the groin. Abdominal MRI showed no visceral abscesses or fistulae.

Despite broad-spectrum intravenous antibiotics, analgesia including morphine and entonox and regular dressings and wound care, her skin condition deteriorated with further discharge and development of a significant spreading ulceration and tissue necrosis. Her left axilla was particularly affected where the friable perimeter of the purulent wound became dusky and violaceous and was felt clinically to be pyoderma gangrenosum after review by a dermatologist, gastroenterologist and colorectal surgeon, all with experience in the care of inflammatory bowel disease patients.

The surgical team were concerned by the rapid progression and tissue destruction around the left axilla and took the patient to the theatre for washout and surgical debridement of non-viable skin of both axillae and groin. Tissue pathology suggested severe acute inflammation with heavy mixed inflammatory cell infiltrate and plentiful neutrophils amid areas of necrosis. Direct immunofluorescence was negative. Despite the presence of epithelial inclusion cysts to suggest a background of hidradenitis, clinical correlation with these results by the dermatologist, gastroenterologist and surgeon favoured pyoderma gangrenosum to be contributory to this acute flare.

Ciclosporin 250 mg twice daily was initiated along with 20 mg oral prednisolone and two doses of 470 mg (5 mg/kg) infliximab which resulted in rapid improvement in the wounds. Infliximab was stopped after the second dose due to wheeze and shortness of breath. This was felt secondary to drug hypersensitivity from infliximab for acute severe ulcerative colitis several years before.

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Her wounds continued to improve after 2 months of ciclosporin and a reducing course of steroids, but an elevation in blood pressure required ciclosporin dose reduction to 100 mg twice daily. This resulted in a flare in her right axilla for which minocycline 100 mg once daily had little effect, and the patient was admitted again 3 months after her debridement with deterioration of her skin at all three sites and severe associated pain.

Intravenous antimicrobial therapy and 40 mg once daily prednisolone improved symptoms, and the decision was made to stop ciclosporin and start methotrexate 25 mg weekly subcutaneously in preparation for further biological therapy. Given her previous excellent response to anti-TNF therapy, we started adalimumab with induction of 160 mg/80 mg followed by maintenance of 40 mg every 2 weeks. Two months into adalimumab therapy, her skin had markedly improved with reduction in pain, minimal skin lesions and increased self-confidence and quality of life. At the most recent review, the patient continues to improve with ongoing healing of all skin wounds and little in the way of active inflammation.

An association between inflammatory bowel disease and neutrophilic dermatoses is already well known. Pyoderma gangrenosum, suppurative hidradenitis, aseptic abscess syndrome and Sweet syndrome have all been observed alongside inflammatory bowel disease but more frequently affecting Crohn's patients [1, 2]. Our patient's lack of deep visceral abscesses and more chronic dermatological history coupled with her pathology excluded aseptic abscess syndrome and Sweet's syndrome, respectively. Raised p-ANCA in our patient is more likely to be related to her ulcerative colitis and not her dermatological problems, particularly with negative direct immunofluorescence of skin biopsies. Furthermore, concomitant suppurative hidradenitis and pyoderma gangrenosum is so rare that a literature review in 2010 [2] identified only 20 such patients, one having underlying Crohn's and none with ulcerative colitis, thus making our patient unique.

A review of the literature in September 2013 identified only two peer-reviewed reports describing PASH syndrome. Braun-Falco et al. [1] reported two cases with no past medical history who demonstrated incomplete resolution with the IL-1 antagonist anakinra and a regime of corticosteroid, azathioprine and skin grafting. Marzano et al. [3] described a patient's vast improvement with infliximab for PASH manifesting 2 years following bowel bypass surgery for obesity. Neither report identified a specific genetic mutation for PASH, in contrast to a common point mutation in chromosome 15 encoding for PSTPIP1 binding protein in all reported cases of PAPA syndrome [1]. From this, our patient appears to be the first reported case following colectomy for ulcerative colitis and furthermore the first to be successfully treated with adalimumab.

Our experience of this rare and only recently recognised disease triad provides a first and interesting case for the literature. We acknowledge that genetic studies are lacking, but clinically, our patient satisfies the description of PASH and provides a complex example of its coexistence with ulcerative colitis. Adalimumab may also be a potentially preferable treatment option over infliximab given its convenient subcutaneous administration and, being a human monoclonal antibody, less potential to trigger adverse antibody reactions [4]. We recognise nonetheless that further understanding of PASH syndrome is required to reliably affirm its optimum management; however, we concur with previous authors on the subject that anti-TNF therapies are a viable option.

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