An unusual case of Behçet's syndrome: Triggered by typhoid vaccination?

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ABSTRACT

A case of Behçet's syndrome in a 32-year-old woman occurring shortly after her third vaccination against typhoid fever is described. Scleritis and pyoderma gangrenosum were unusual manifestations of BS that occurred in this case. Treatment benefit was provided by mycophenolate mofetil and etanercept. As bacterial antigens have been proposed as potential triggers for the onset of BS, it is possible that the syndrome was precipitated by typhoid vaccination in this patient.

Case report

A previously healthy 32-year-old Irish woman presented to her local hospital on 31/7/02 with a three-week history of malaise and pain, erythema and swelling over the right shin of such severity that she required a crutch to walk. These findings had been previously diagnosed by her general practitioner as cellulitis and treated with oral antibiotics and a non-steroidal anti-inflammatory drug with some clinical improvement, although the severe leg pain persisted. She then developed two erythema nodosum-like lesions, one on the forearm and one below the right knee. She had severe arthralgia in the right wrist and both knees and ankles. The anti-streptolysin O titre was 800iu/ml. Thus, post-streptococcal erythema nodosum was diagnosed.

She was treated with penicillin and prednisolone 40 mg daily. There was an initial improvement, but following discharge she complained of severe immobility and mottling of the skin of the lower extremities. Prednisolone was discontinued and within days, multiple painful erythematosus lesions appeared on all four limbs associated with pain and swelling of the wrists and left elbow. In addition she developed severe buccal cavity ulceration as well as generalised weakness, malaise, abdominal pain, anorexia and weight loss. She was transferred to our rheumatology unit on 23/8/02.

Four days prior to the onset of her first symptoms she had received typhoid and hepatitis A vaccinations in preparation for a trip to Vietnam. She had previously been vaccinated against typhoid in 1993 and again in 1998. There was no past medical or family history of note. Her only medication was the combined oral contraceptive pill. She was a nurse tutor but had no patient contact. She was a non-smoker and had no history of recent travel or sexual contacts or of intravenous drug use. There was no family history of note. Examination at presentation revealed temperature 38ºC, two oral ulcers without genital ulceration and multiple tender subcutaneous nodules of the upper limbs. Initially, white cell count (WCC) was 12.3 x 10^9/l (neutrophilia), haemoglobin 12.7g/dl, platelet count 205 x 10^9/l, ESR 54mm/hr, CRP350iu/l (normal < 6.0) and normal renal and liver profiles. ECG and chest radiograph were normal.

Her condition worsened following admission. She was febrile over the next 5 days with temperature up to 39ºC. She developed further red, tender palpable skin lesions affecting face, hands, wrists and lower limbs all of which became rapidly bullous or pustular in appearance (Fig. 1) and some of which ulcerated. These were felt to represent bullous pyoderma gangrenosum. There was synovitis in multiple joints and dactylitis (with both synovitis and tenosynovitis) affecting all toes and most fingers and worsening oral ulceration. She developed a painful red right eye. She required large doses of opioid analgesia to control her symptoms. Repeat

laboratory testing showed WCC 21.43 x 10^9/l (neutrophilia), haemoglobin 9.1 g/dl (normochromic, normocytic), platelet count 753 x 10^9/l, ESR 99 mm/hr, CRP 322iu/l. ANCA, ANA, RF, cryoglobulins and complement were normal as was serology for infectious organisms including brucella, CMV, EBV, hepatitis A, B and C. Serum protein electrophoresis showed a diffuse increase in globulin fraction consistent with acute phase response. HLA-B51 was positive. Multiple cultures of blood and skin lesions were negative. Radiographs of hands, wrists and sacroiliac joints, echocardiogram, whole body radionuclide bone scanning and whole body MRI were normal. Pathergy test was negative. Scleritis of the right eye was diagnosed by the ophthalmology service. Slit-lamp examination was delayed for a number of weeks after high dose steroids were commenced because the patient's degree of debility was such that she could not sit in front of the slit lamp. However, when the examination was eventually performed no evidence of uveitis or retinal vasculitis was detected. Skin biopsy is shown in Figure 2. Colonoscopy revealed multiple superficial ulcers less than 2 cm in size on a generally hyperaemic mucosa in the recto-sigmoid colon. Colonic biopsy showed evidence of neutrophilic infiltration with reactive endothelial changes consistent with vasculitis.

She was treated with corticosteroid eye drops, dapsone 100mg daily, colchicine 0.5mg bid, and prednisolone 120mg daily. Although there was some improvement in her symptoms over the next 2 weeks with fever settling and ESR and CRP decreasing, new skin lesions were still appearing. As her steroid dose was gradually reduced dapsone was discontinued due to the development of methaemoglobinaemia and abnormal liver function tests and mycophenolate mofetil (MMF) 1g bid was commenced instead. She continued to improve slowly and her oral ulcers and cutaneous ulcers healed and the scleritis resolved. The ESR and CRP normalised approximately 6 weeks after starting steroids. Azathioprine (AZA) 100mg daily was added after the diagnosis of BS was established and liver function test abnormalities resolved. Pain and mobility slowly improved with physiotherapy and analgesics were slowly weaned.

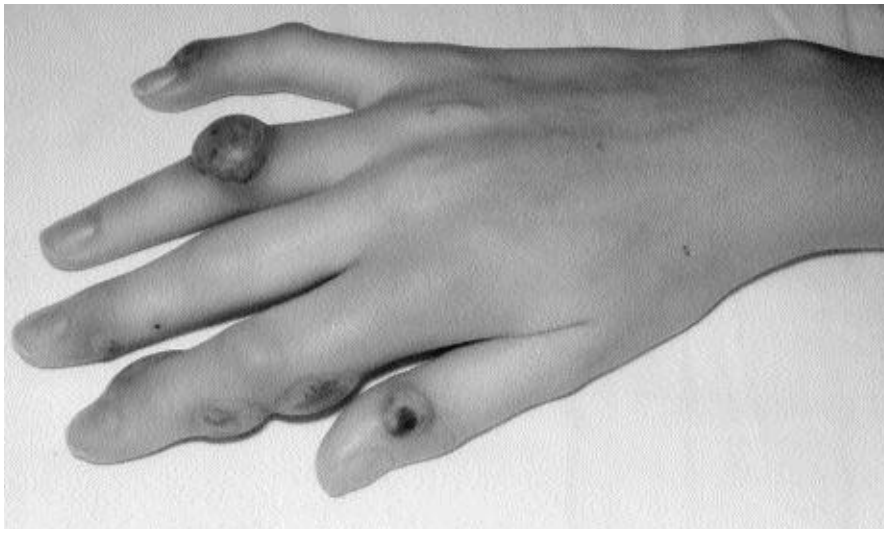

Fig. 1. Multiple pustular and bullous skin lesions affecting the right hand with erythema and swelling, particularly at the second metacarpophalangeal and proximal interphalangeal joints.

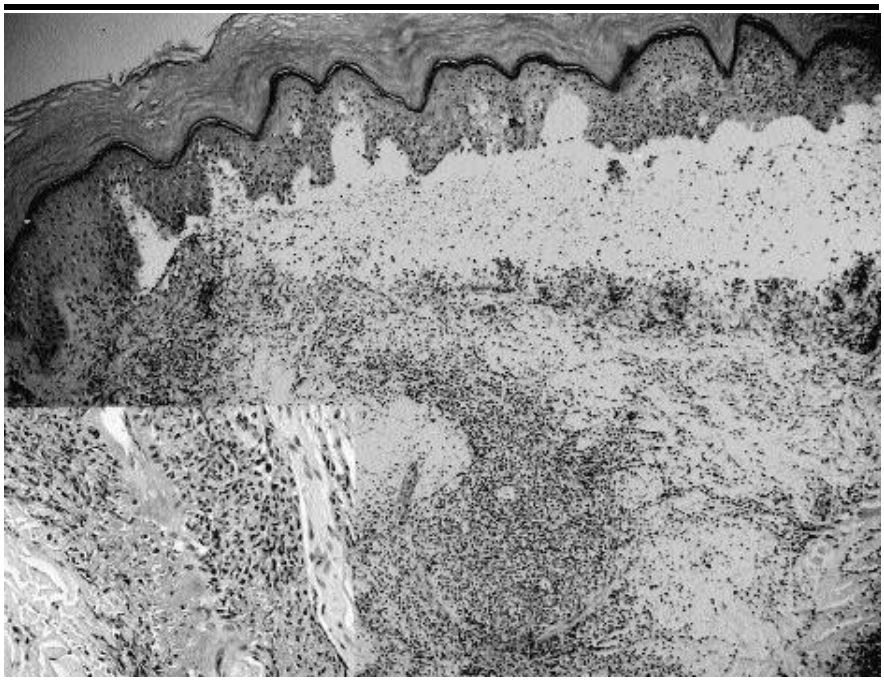

Fig. 2. Punch biopsy demonstrating a sub-epidermal blister overlying a neutrophilic dermatosis with neutrophilic vasculitis (inset) (Hematoxylin-Eosin, original magnification X 200, inset X 400).

She returned to work and medication was tapered to prednisolone 3mg daily, AZA50mg daily and MMF. Following a reduction of the MMF dose to 500mg bd in March 2004, she developed a recurrence with symptoms of oral ulceration, slit-lamp documented uveitis, erythema nodosum and arthralgias. She did not mount a significant acute phase response. AZA was discontinued and etanercept 25mg twice weekly was commenced. She is currently asymptomatic receiving MMF 1g bd, etanercept and prednisolone 5mg daily.

Discussion

This patient was diagnosed with Behçet's syndrome because she had severe oral ulceration, scleritis, arthritis, colonic inflammation and cutaneous lesions. She was also HLA-B51 positive. As is common in northern Europe, the

pathergy test was negative. Pyoderma gangrenosum is a recognised feature of BS (1) and there are a number of reports in the literature (2-6). Many of the clinical findings in this case could occur with chronic inflammatory bowel disease, Crohn's disease in particular. The presence of vasculitis without granuloma formation on colonic biopsy as well as the lack of perianal disease, stricture formation or deep mucosal ulceration, makes Crohn's disease unlikely in this case. The presence of vasculitis on skin biopsy excluded the neutrophilic dermatoses from the differential diagnosis. The presence of vasculitis and prominent articular manifestations outrule Steven-Johnson syndrome.

MMF has reported efficacy in the treatment of refractory pyoderma gangrenosum (7-9); it was commenced because of the severe nature of the bullous pyoderma gangrenosum-like lesions which were the main clinical problem of this patient and were responding very slowly to high-dose prednisolone, colchicine and dapsone. MMF also has a favourable side effect profile compared to other potential therapies. While MMF provided benefit in the treatment of BS in our patient in terms of a steroid-sparing effect and the control of disease activity, previous experience was less favourable (10). However this trial had enrolled just 6 patients and does not prove a lack of efficacy of MMF in the treatment of BS. Because of concerns regarding the ability of MMF to maintain remission in BS, AZA was added approximately six weeks later, as it is a standard treatment for BS. This treatment regimen was well tolerated and maintained remission for 18 months in this patient. In fact, relapse occurred only as the MMF dose was tapered to 1g daily. Evidence to support a role for etanercept in the treatment of BS is discussed by Sfikakis (11). The resolution of symptoms following its introduction in this patient also supports a potential therapeutic role for etanercept in BS.

There is interest in the potential role of bacterial antigens with cross-reactivity to human peptides in the pathogenesis of BS, reviewed by Direskeneli (12). *Escherichia coli* and *Staphylococcus aureus* and in particular, streptococcal species, have all been implicated. It has also been proposed that bacterial heat shock proteins, which are highly conserved, may play a role in BS (12). There have been previous reports in the English language literature of vaccine-associated vasculitis, predominantly following influenza and hepatitis B vaccination (13-18), although a causal link has not been established. There has also been a report of a case of BS occurring in association with a polyvalent vaccine (19).

The patient described above received typhoid vaccine (containing the Vi antigen) four days prior to the onset of her symptoms. This was in fact her third time to be vaccinated against typhoid within 9 years. As a variety of bacterial antigens seem to induce immunologic responses in BS (12), it is at least possible that the typhoid antigen triggered the onset of BS in this HLA-B51 positive patient. There is no *in vitro* data to support the potential role of specific typhoid antigens in BS. Toivanen *et al.* noted no increase in antibodies to somatic or flagellar salmonella antigens in patients with BS, as measured by bacterial agglutination (20). Typhoid has been reported in association with BS in one previous case (21) and there have been 3 other reports of vasculitis associated with salmonella infection (22). It is interesting to note that the geographic distribution of greatest prevalence of BS roughly corresponds to the area of overlap of typhoid endemicity (23) and HLA-B51 positivity (24).

A further issue in this case is that this patient's identical twin sister is HLA-B51 positive, as expected. She has been advised of the possible risk associated with typhoid vaccination and not to undergo typhoid vaccination unless it is felt absolutely necessary. Whether other vaccines containing bacterial antigens also pose a risk to our patient or her sister is unclear.

While this is a single case report, it raises an interesting question about the possible role of typhoid antigens in triggering BS in genetically susceptible individuals. Given the existing data that suggest potential involvement of a variety of bacteria, this putative trigger is likely to be a highly conserved bacterial antigen with potential cross reactivity to human peptides. It is tempting to speculate that differences in the bacterial antigens triggering BS might account for the observed variation in disease expression between and within populations.

Discussion

by Prof. Hasan Yazici (Head, Behçet's Disease Research Unit, University of Istanbul)

It was Dr. George Ehrlich, a long-time student of Behçet's disease, who first suggested that we should probably differentiate between Behçet's syndrome and Behçet's disease (25), reserving the designation 'disease' for the entity one sees in areas where Behçet's is endemic such as Turkey or the Far East and using the term 'syndrome' to these cases in areas where the condition is encountered only sporadically.

I think the case presented here offers a good example of Dr. Ehrlich's contention. This patient would in strict terms fulfil the international criteria for classification (26) with arthritis, eye disease, skin lesions and intestinal ulcers in the almost constant presence of oral ulcers. Her being HLA-B51 positive provides further support for the diagnosis. On the other hand, scleritis is rarely associated with Behçet's, especially in the absence of any signs of uveitis. Pyoderma gangrenosum, with or without bullae, is also very uncommon in the endemic setting.

Some years ago our British colleagues conducted a study comparing the clinical features of Behçet's as seen in the UK and in Turkey (27). Using cluster analysis, they came to the conclusion that the disease presentation was similar between the two countries. I feel that it is now time to formally re-test this hypothesis not only by comparing the different organ systems involved in different geographic areas, but also more closely comparing the type of involvement in any one organ system. The results will not, in all probability, give us any immediate clues to the riddle of Behçet's, but will surely bring forward some very stimulating questions that might set us on the right path to solve this riddle.

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