**Burkholderia cepacia** complex and limited cutaneous vasculitis in patients with cystic fibrosis: a case series

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**Lesson**

There is a high association of reactive skin presentations, mainly limited cutaneous vasculitis in patients with cystic fibrosis and **Burkholderia cepacia** complex chronic infection. This may be due to raised levels of circulating inflammatory mediators.

**Keywords**
cystic fibrosis, dermatology, microbiology, pathology, respiratory medicine, rheumatology, vasculitis

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The local cystic fibrosis database was used to identify patients (1992–2012) with **Burkholderia cepacia** complex and cutaneous involvement using the search terms ‘vasculitis’, ‘skin’ and ‘other complication’. In our large adult cystic fibrosis unit of nearly 600 patients, the prevalence of infection with chronic **Burkholderia cepacia** complex is 5% (n = 30). The prevalence of cutaneous involvement in patients with **Burkholderia cepacia** complex was 23.3% (n = 7). Here, we present the full details of four of these patients (Table 1).

### Case 1

A 26-year-old female with **Burkholderia cenocepacia** presented with a two-month history of worsening fixed purpuric rash on the lower legs (Figure 1). Skin biopsy confirmed leucocytoclastic vasculitis. She was treated with dapsone initially without improvement. On commencement of oral prednisolone, there was minimal improvement, which remained stable. Following this, she was managed with topical protopic 0.1%.

### Case 2

A 23-year-old female with **B. cenocepacia** developed an erythematous maculopapular rash on the lower legs with associated arthropathy of her finger joints. This was clinically felt to be reactive leucocytoclastic vasculitis and a biopsy was not conducted. The vasculitis did not respond initially to oral prednisolone, and she was then commenced on azathioprine and the rash responded to this. Two years later, she died following a severe infective exacerbation of her chest.

### Case 3

A 32-year-old male with a history of **B. cenocepacia** and **Burkholderia multivorans** developed an erythematous rash on the lower legs associated with an infective exacerbation of his chest. The rash resolved leaving grey discolouration but would occasionally flare up in the summer months. The biopsy showed features of capillaritis, and he was managed with topical steroids and compression hosiery.

### Case 4

A 26-year-old female with **B. cenocepecia** presented with a history of recurrent small joint pains in association with intermittent painful erythematous nodular rash on the lower legs. This came on at the onset of an infective exacerbation of her chest. Biopsy confirmed erythema nodosum. Other causes of erythema nodosum were excluded, and she did not respond to Non-steroidal anti-inflammatory medications. Her symptoms continue to relapse in association with infective exacerbations of her chest.

Of the remaining patients (n = 3), one presented with an erythematous rash on the lower legs and another had a purpuric rash on the lower legs and both were diagnosed clinically as leucocytoclastic vasculitis by a dermatologist. The third patient presented with purpuric areas and blistering of the lower legs which was confirmed as leucocytoclastic vasculitis on biopsy.
Table 1. Demographic, diagnosis, management and outcomes of patients.

| Patient number | 1       | 2       | 3       | 4       |
|----------------|---------|---------|---------|---------|
| Age at onset of rash (years) | 26      | 23      | 32      | 26      |
| Sex            | Female  | Female  | Male    | Female  |
| Ethnicity      | Caucasian | Caucasian | Caucasian | Caucasian |
| Genotype       | F508/F508 | F508/F508 | F508/F508 | F508/F508 |
| Co-infection   | None    | PSA+SA  | None    | PSA     |
| Appearance of rash as described | Intermittent urticarial rash and another rash on legs described as confluent purple lesions + fixed purpuric lesions | Erythematous maculopapular rash/morbilliform | Erythematous rash + swollen legs background of grey discoloration and post inflammatory change | Painful rash affecting lower legs |
| Diagnosis on biopsy | Leucocytoclastic vasculitis | No biopsy | Capillaritis | Erythema nodosum |
| Associated joint pains | No | Yes | No | Yes |
| Treatment       | Dapsone  Then switched to oral steroids  Then switched to protopic 0.03% topically | Oral steroids  Then switched to azathioprine | Compression stockings, Non-steroidal anti-inflammatories (Non-steroidal anti-inflammatory medications) and Betnovate cream | Trial of NSAIDs but no ongoing treatment |
| Outcome of cutaneous lesions | No change with dapsone or oral steroids. Improvement with topical protopic but no complete resolution | No response to steroids. Rash responded to azathioprine and then resolved. Azathioprine stopped | Improvement with Non-steroidal anti-inflammatory medications and topical betnovate but no resolution | Relapsing and remitting, no clinical association with infective exacerbations |

SA: Staphylococcus aureus; PSA: Pseudomonas aeruginosa.
Overall, two patients had biopsy proven leucocytoclastic vasculitis, three were clinically diagnosed with vasculitis but did not have biopsy confirmation and two had biopsies, which revealed other pathologies (erythema nodosum and capillaritis), giving an overall prevalence of cutaneous vasculitis in patients with *Burkholderia cepacia* complex of 16.7%. Out of the five patients with vasculitis, three had a raised ESR/CRP ratio.

There was no evidence of renal involvement in any patient – all had a negative urine dipstick and normal serum creatinine. The antinuclear antibody and anti-neutrophil cytoplasmic antibody were negative in all patients apart from one with biopsy proven leucocytoclastic vasculitis who had a transiently positive anti-neutrophil cytoplasmic antibody. Antistreptolysin O titre was tested in only two out of the five patients and was negative.

Mean forced expiratory volume$_1$ was 30% (range: 18–55) of the predicted value. In four patients (57%), the forced expiratory volume$_1$ was lower at the time of presentation with rash compared to the baseline forced expiratory volume$_1$ values for the previous two years.

All patients received antibiotics for a presumed pulmonary exacerbation at onset of the rash. Three patients received specific treatment for vasculitis (prednisolone ± additional immunosuppressive) after non-resolution of the rash.

**Discussion**

Cutaneous vasculitis represents a specific pattern of inflammation affecting the vessels in the dermis.$^1$ Its prevalence in the general population is difficult to estimate as not all cases are biopsied; however, the estimated incidence of biopsy proven cases is thought to be between 15 and 60 patients per million per year.$^2$

Limited cutaneous vasculitis tends to present on the lower limbs and can be associated with arthralgia.$^{3,4}$ In patients with cystic fibrosis, it has been described in association with respiratory infections – including *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenza* – with several antibiotics and also with pancreatic enzyme supplements.$^4$ These associations are thought to result in antigen excess, which in turn causes a rise in circulating immune complexes, complement activation and blood vessel wall damage.$^1$

To our knowledge, vasculitis in association with *Burkholderia cepacia* complex has not been reported. Clinical observations had suggested a proportionately high frequency of cutaneous vasculitis in this cohort. We report seven cases of cystic fibrosis patients with dermatological complications associated with *Burkholderia cepacia* complex, of which five were cutaneous vasculitis. Importantly, the vasculitis was limited as there was no evidence of other organ involvement. These data suggest that the prevalence associated with *Burkholderia cepacia* complex is high (16.7%). Putatively, this may be due to the exuberant inflammatory state associated with *Burkholderia cepacia* complex, particularly *B. cenocepacia*. Out of the 30 patients in our cohort with *Burkholderia cepacia* complex, 15 (50%) have *B. cenocepacia*, 13 (43%) have *B. multivorans* and two (7%) *Burkholderia cepacia*. All of our patients in this case series had *B. cenocepacia*, providing further support for the association between limited cutaneous vasculitis and an exuberant inflammatory state.

The literature on cutaneous vasculitis in cystic fibrosis mainly describes the expected typical purpuric rash on the lower legs; however, maculopapular rashes have also been described.$^3$ This may reflect an early stage of the vasculitis prior to blood vessel wall damage and red cell extravasation, characterised by palpable purpura. Bullae and ulceration may be present in severe cases.

As mentioned previously, medications including antibiotics and pancreatic supplements are estimated to be the cause in up to 15% of cutaneous vasculitis.$^1$ In patients with cystic fibrosis, isolating a causative drug can be difficult due to polypharmacy and recurrent requirement for antibiotics. In our cohort, the symptoms of vasculitis preceded any new medications.

Henoch-Schonlein purpura is an important differential to consider, as it tends to be self-limiting and treatment is mainly supportive. Antistreptolysin O
titres can be positive in up to 50% of patients with cutaneous vasculitis in general. Interestingly, β-haemolytic Streptococcus is rarely isolated from the sputum of patients with cystic fibrosis.1

The associated feature of joint pains in five of our patients is interesting, and is also echoed in the cystic fibrosis literature with various cases of cutaneous vasculitis.5,6 An episodic arthropathy is commonly described; the underlying mechanism has not been fully elucidated but it probably shares a common inflammatory pathway with cutaneous vasculitis, as both are characterised by raised circulating immune complexes, particularly during pulmonary exacerbations.5 None of our patients had a persistently positive serum antineutrophil cytoplasmic antibody. This is in contrast to patients with chronic P. aeruginosa infection, where antineutrophil cytoplasmic antibody (IgA/IgG) against bactericidal permeability increasing (BPI) protein is often found.7

Cystic fibrosis patients with Burkholderia cenocepacia complex have a varied clinical outcome from asymptomatic carriage to rapid forced expiratory volume1 decline.8 B. cenocepacia is of particular importance, as it demonstrates increased virulence and worse outcomes.9 Although some studies have demonstrated an association between forced expiratory volume1 decline and vasculitis,3 we were unable to confirm this due to the limited number of patients in our cohort.

Treating cutaneous vasculitis should be aimed at treating the underlying cause where possible. Eight per cent of our cohort did not respond to treatment of a pulmonary exacerbation and were treated with oral steroids alone, or in conjunction with azathioprine or ciclosporin and demonstrated modest results. There is evidence in the literature for all of the treatments used1,3,4,10; however, immunosuppressive agents especially in cystic fibrosis must be used with caution due to the theoretical risk of attenuating host defence mechanisms to infections. In general, potent topical steroids in combination with oral steroids, dapsone or colchicine are considered first-line treatments for patients with ongoing cutaneous vasculitis.1

In conclusion, we have presented a case series of limited cutaneous vasculitis and two cases of other reactive skin presentations in association with Burkholderia cenocepacia complex. Our data suggest a high prevalence of skin complications, which is probably due to high levels of circulating inflammatory mediators with chronic Burkholderia cenocepacia complex infection. We recommend a systematic approach to patient evaluation including screening for infectious triggers, drugs and systemic involvement, and early lesional skin biopsy for histology and immunofluorescence to guide treatment.

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