Original articles

Chronic suppurative lung disease with associated vasculitis

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Summary

We report a patient with chronic bronchiectasis who developed systemic vasculitis. The patient was initially treated with immunosuppression; however, the addition of antibiotic therapy improved control of her vasculitis and the need for immunosuppression was reduced. Chronic bronchial suppuration may have an aetiological role in the pathogenesis of this condition.

Keywords: bronchiectasis, systemic vasculitis

Introduction

Vasculitis associated with chronic suppurative lung disease has been reported in a few cases of bronchiectasis and cystic fibrosis.^{1–7} We report the case of a 47-year-old female with chronic bronchiectasis who presented with cutaneous and mesenteric vasculitis requiring small-bowel resection, whose vasculitis appeared to improve with control of her chest condition. We also review the literature regarding the association between these conditions and consider the differential diagnosis, pathogenesis and management of vasculitis in this situation.

Case report

The patient, a 47-year-old female developed bronchiectasis following an episode of whooping cough at 10 years old. In March 1991 she presented with a one-month history of a migratory papular, non-itchy skin rash over the dorsa of both hands, her forearms and thighs, diagnosed as chronic urticaria. Two months later she complained of intermittent joint pain and swelling. A diagnosis of palindromic rheumatism was made and treatment with ibuprofen achieved no improvement. These symptoms persisted over the next few months and in October 1991 she was admitted with a four-week history of crampy abdominal pain, diarrhoea and a 7-kg weight loss. A small bowel series suggested a diagnosis of Crohn's disease affecting her terminal ileum and she was started on 5-aminosalicylic acid 2 g and prednisolone 30 mg daily with symptomatic improvement.

Two weeks following discharge she was readmitted with a perforation of her proximal jejunum diagnosed at emergency laparotomy. On inspection, the vessels to this area were thrombosed and no nodules were visible; the

remaining bowel, including the distal ileum, appeared normal. She underwent resection of 20 cm of jejunum and had an uneventful post-operative recovery. Histological examination of the specimen adjacent to the perforation showed extensive mucosal ulceration with numerous fissure ulcers extending into the submucosa, no granulomata were seen. Arterioles within the bowel wall and adjacent mesentery showed arteritis with inflammation of the wall, recent and recanalizing thrombi and focal disruption of the internal elastic lamina (figures 1 and 2).

Other investigations during this admission showed a normal urinalysis, serum creatinine and white cell count, while her eosinophil count was 1%. Complement factors C3 and C4 were 0.54 g/l (0.75–1.5) and 0.09 g/l (0.09–0.34), respectively. Tests for rheumatoid factor, antinuclear antibodies and hepatitis B surface antigen were negative. Antineutrophil cytoplasmic antibodies were tested using indirect immunofluorescence as described by Wiik⁸, myeloperoxidase antibodies (MPO)

Figure 1 (H and E $\times 24$) Sharply demarcated mucosal ulceration of small intestine with focal fissure ulcers

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Figure 2 (H and E × 100) Serosal arteriole (bold arrow) showing arteritis with inflammation of vessel wall, focal destruction of the internal elastic lamina and recanalization of thrombus in the lumen

were tested by ELISA (Biocarb ELISA). pANCA was positive 1/20, MPO antibody was 19% (<20%). A diagnosis of mesenteric vasculitis was made and the patient was commenced on prednisolone 40 mg and cyclophosphamide 200 mg daily.

This regime was continued for the next seven months during which time she had no further abdominal or joint symptoms; her rash, however, persisted although it was less frequent and florid than before. Her daily sputum volume did not change on immunosuppressants. Attempts to reduce her immunosuppression persistently resulted in her rash worsening, and she was therefore referred to the Department of Rheumatology for further investigation in September 1992. A biopsy of the rash confirmed a leucocytoclastic vasculitis; immunofluorescence revealed IgM and C3 deposits along the basement membrane and blood vessels. Culture of her sputum grew *Pseudomonas* spp, no acid-alcohol fast bacilli were grown. Other investigations confirmed normal renal function, cryoglobulins were not detected. IgG was 13.5 g/l (7–14), IgA 4.39 g/l (0.8–4.0), IgM 0.82 g/l (0.45–2.0), and pANCA 1/80; anti-MPO was not detected. CT scan of the chest showed diffuse multilobular bronchiectatic changes in both lung fields. She was initially commenced on a seven-day course of intravenous ceftazidime followed by continuous oral co-trimoxazole 400 mg daily.

Since commencement of antibiotics she has experienced a dramatic improvement in the frequency of her rash with no new lesions having developed in the past nine months; she

has had no further abdominal or joint symptoms. Her daily sputum volume has also reduced. In view of this improvement, her immunosuppression has been reduced to cyclophosphamide 50 mg daily monotherapy. In this period her antibiotic has been changed approximately every three months and she is currently on doxycycline 100 mg/day, with continued control of her condition.

Discussion

The association of vasculitis with chronic suppurative lung disease has been reported both in patients with cystic fibrosis and acquired bronchiectasis.^{1–7} Our patient had a definite history of onset of her bronchiectasis after an episode of whooping cough when aged 10 years old. She has not had a sweat test but the absence of typical features expected in cystic fibrosis on her small bowel histology accords with acquired bronchiectasis.⁹

When such patients develop vasculitis, several differential diagnoses need to be considered namely, drug-induced vasculitis,¹⁰ cryoglobulinaemia,¹¹ and hypergammaglobulinaemic purpura,¹² the principal features of which are summarised in table 1. Our patient was on no medication prior to the onset of her rash in March 1991 and her ibuprofen, started in June 1991, was stopped several weeks prior to her developing abdominal pain. She was persistently rheumatoid-factor-negative and had neither cryoglobulins or marked elevation in globulins during her illness, ruling out any of the above associations. Chronic suppurative lung disease can also be related to vasculitis without any of the above identifiable associations^{1–7} and our computer search of the literature up to September 1993 revealed 28 other cases, summarised in table 2, three of which were contained in a series by Pinching *et al* who noted an association between Wegener’s granulomatosis and preceding bronchial or sinus suppuration.¹³ This chronic suppurative lung disease associated vasculitis is not simply a cutaneous vasculitis since, including our case, 11 and possibly 14 (33–48%) of the cases recorded had a systemic vasculitis, ie, vasculitis involving two or more organs (table 2).

The pathogenesis of this form of vasculitis is not fully known. Immunological changes in association with bronchiectasis are well documented; 80% have elevated immuno-

Table 1 Clinical features and investigations in the differential diagnosis of vasculitis associated with bronchial suppuration

Diagnosis	History	Physical signs	Investigations
Drug-related vasculitis ¹⁰	Occurs during administration or within 10 days of stopping drug ²⁹	Skin rash Fever in 80% of systemic cases ²⁹	Peripheral eosinophilia (40%)
Mixed cryoglobulinaemia ¹¹	Arthralgia, weakness, Raynaud’s phenomenon	Palpable purpura Leg ulcers Hepatosplenomegaly Glomerulonephritis	Rheumatoid factor positive Cryoglobulins
Hypergammaglobulinaemic purpura ¹²	Long-history of primary condition: ‘terminal phenomenon’ ³⁰	Purpura of extremities	Rheumatoid factor positive Markedly elevated ESR, IgA, IgG

Table 2 Clinical and laboratory features of vasculitis related to bronchial suppuration from literature review

Diagnosis	Number of cases	Mean duration at onset of vasculitis (years)	Systemic involvement	Immunosuppressant treatment	ANCA detected (number/number tested)	Immune complexes detected (number/number tested)
acquired bronchiectasis ¹	4	23	Henoch-Schonlein purpura (HSP) (1)	prednisolone (1)	N/A	4/4
acquired bronchiectasis ²	2	11	Wegener's granulomatosis (1) Microscopic polyarteritis (1)	prednisolone + cyclophosphamide (2)	2/2	1/2
acquired bronchiectasis ³	1	31	Systemic hypersensitivity vasculitis (1)	prednisolone + cyclophosphamide (1)	0/1	1/1
acquired bronchiectasis ¹³	3	Not recorded	Wegener's granulomatosis (3)	prednisolone + cyclophosphamide (3)	N/A	N/A
cystic fibrosis ⁴	12	22.3	cerebral (1), HSP (1), + possible HSP (1)	prednisolone (3) prednisolone + azathioprine (1) prednisolone (1)	4/10	3/4
cystic fibrosis ⁵	3	18	Systemic necrotizing vasculitis (1)		N/A	1/1
cystic fibrosis ⁶	2	16	? 2 (skin rash and microscopic haematuria)	None	N/A	1/1
cystic fibrosis ⁷	1	18	—	None	N/A	N/A

N/A = not available.

globulins,¹⁴ approximately 50% have a positive rheumatoid factor,¹⁴ and up to 50% have increased immune complexes.¹⁵ Clinically, an association with other autoimmune diseases is also recognised.^{16–18} Immune complexes are believed to be important in the pathogenesis of this vasculitis¹ although Moss *et al*¹⁹ have shown that, despite a high prevalence of circulating immune complexes in patients with bronchiectasis, there was little evidence of systemic complement activation suggesting that, alone, their pathogenicity may be limited. Many properties of immune complexes do, however, affect their pathogenicity including their size and lattice structure, their ability to bind complement, the antigen:antibody ratio and the antigen itself. In bronchiectasis the bacterial flora is the major antigenic source with tissue products playing a less important role.^{19,20} Over time this can evolve from eg, *Staphylococcus aureus* to *Pseudomonas* spp. With this change in bacterial flora, a critical change in the antigenic component of the complexes may occur which render previously harmless complexes pathogenic. Some bacteria may induce such a change more readily than others and this may explain the late onset of vasculitis in most cases. Cytokines may also be important as tumour necrosis factor alpha (TNF- α) levels are elevated in patients with infective exacerbations of cystic fibrosis.²¹ The effects of this cytokine include adhesion molecule expression, particularly ELAM-1, secretion of platelet activating factor, IL-1 and IL-8 from endothelial cells and ‘priming’ of neutrophils enhancing their production of reactive oxygen species. It can also be directly damaging to endothelium.²² Cytokines would therefore promote accumulation of activated inflammatory cells close to a potentially weakened endothelium with resultant vascular injury.

Finnegan *et al*⁴ noted that 40% of patients with cystic fibrosis and vasculitis had anti-neutrophil cytoplasmic antibodies (ANCA) present. Including our case, seven out of 14 cases in which ANCA was tested were positive.^{2–4} Five were cytoplasmic pattern (c-ANCA)^{2,4} and one was perinuclear staining (p-ANCA).² Our patient was p-ANCA positive but anti-MPO negative, indicating an alternative antigenic specificity.²³ ANCA in this setting may simply be a phenomenon secondary to chronic neutrophil destruction² since others have noted ANCA in patients with cystic fibrosis without evidence of vasculitis.²⁴ It has, however, been suggested that ANCA may be pathogenic in vasculitis, either by recognition of endothelial-bound ANCA autoantigens,²⁵ or by enhancing oxyradical production from neutrophils, the latter occurring after the cells have been ‘primed’ by cytokines, eg, TNF- α .²⁶ The cytokines present in patients with an exacerbation of bronchiectasis, together with circulating ANCA may therefore represent an *in vivo* model of the pathogenesis of ANCA-related vasculitis proposed by Falk and Jennette²⁶ and hence the apparent coincidental finding of ANCA in uncomplicated cystic fibrosis may put such patients ‘at risk’ of vasculitic complications. Finally, vasculitis commonly occurs at areas of turbulent flow or increased hydrostatic pressure, factors which facilitate immune complex deposition.²⁷ In Hilton’s series two patients had cor pulmonale, with improvement of the vasculitis in one following treatment for this alone.¹ The increased venous pressure induced by this complication may explain this and also the late onset of vasculitis in most cases.

Management of this condition reflects its variable extent and course, in some cases the cutaneous vasculitis has resolved spontaneously, in others systemic vasculitis has run a

fulminating and rapidly fatal course. Twelve cases reviewed had disease of sufficient severity to indicate immunosuppressive therapy, only one of whom did not improve.⁴ Immunosuppression can also improve chest symptoms when they are presumably caused by immune complexes or inflammatory mediators.^{3,21} Hilton *et al* described one case with recurrent cutaneous vasculitis which improved on prophylactic antibiotics.¹ In parallel with the clinical improvement, the levels of circulating immune complexes were also reduced. Fradin *et al* noted a similar dramatic response to intravenous antibiotic therapy in their patient with cutaneous vasculitis.⁷ Our case also had a dramatic improvement in her rash following intensive antibiotic therapy which has now been maintained for more than nine months on prophylactic antibiotics. The improvement is related to antibiotic chemotherapy and not to the proposed beneficial effect of co-trimoxazole on vasculitis,²⁸ as it is sustained on alternative regimes. If this condition can be significantly improved by control of the chest sepsis it may be postulated that a 'cure' could be achieved by surgical resection of the affected segment of

lung. As with our patient, most will have diffuse involvement, ruling out such intervention, nevertheless this option may be available to a few selected patients. Other measures to optimise concurrent problems, eg, cor pulmonale, also seems to be of benefit in some patients.¹

Therefore, in patients with vasculitis associated with chronic suppurative lung disease, the differential diagnosis described above should be considered and systemic involvement should be carefully sought. In cases with systemic vasculitis, immunosuppression with steroids and cyclophosphamide will control disease without any detrimental effects on lung function. Treatment with appropriate antibiotics has a useful role in some cases, presumably by reducing the antigenic load and, as a result, the volume of immune complexes produced. This case further demonstrates that antibiotic prophylaxis may help control the vasculitis and also reduce the need for systemic immunosuppression.

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