## DISCUSSION

In microscopic polyangiitis, necrotising glomerulonephritis is the most common abnormality and pulmonary capillaritis often occurs. Perinuclear ANCA are present in more than 60% of patients, and antimyeloperoxidase antibody is closely allied.[1] Gastrointestinal involvement is usually mild and there is no report of extended colonic ulcerations and haemorrhage.[2] In addition, colonic biopsy disclosed crypt abscess, which can be found in ulcerative colitis, infectious colitis, radiation induced colitis, and graft versus host disease.[3–5] However, such a finding has not been reported previously in patients with microscopic polyangiitis. Ulcerative colitis was diagnosed initially according to the colonoscopic and pathological findings. Pulmonary vasculitis is very rare in patients with inflammatory bowel diseases.[6] Renal disease with necrotising glomerulonephritis is not commonly seen in patients with ulcerative colitis.[7] In addition, antimyeloperoxidase antibody is usually not detected in such patients.[8] The clinical course of this patient who had lung and renal manifestations did not favour a diagnosis of ulcerative colitis. The final diagnosis was microscopic polyangiitis with gastrointestinal involvement.

Extended colonic ulcerations with haemorrhage have not been reported previously in patients with microscopic polyangiitis. Vasculitis should be considered for differential diagnoses of colonic ulcerations, especially when the presentation is atypical, to avoid delay of prompt treatment.

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# Severe digital ischaemia treated with phosphodiesterase inhibitors

**C R Kumana, G T Y Cheung, C S Lau**

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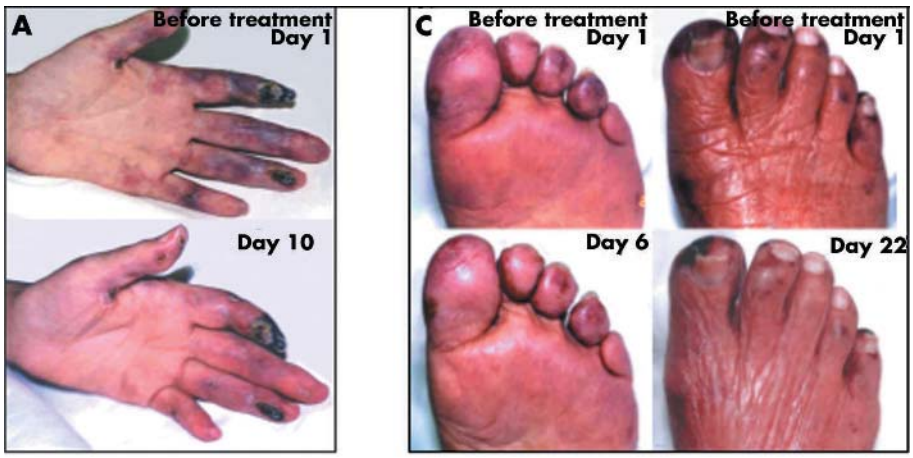
Pulmonary hypertension is associated with autoimmune diseases, giving rise to digital ischaemia, including Raynaud's phenomenon (RP). As sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor, relieves the pulmonary hypertension,[1] we suggested that it might also benefit digital ischaemia and RP symptoms. This report describes the impact of oral sildenafil (Viagra, donated by Pfizer HK) on three women with autoimmune disease and progressively severe digital ischaemia, despite treatment with a variety of drugs, including intravenous iloprost (fig 1). All patients gave written informed consent to try this off-label treatment.

## CASE REPORTS

A 42 year old woman with dermatomyositis ''sine myositis'' and thyrotoxicosis (case 1) taking prednisolone, hydroxychloroquine, and carbimazole, experienced regression of troublesome RP and ischaemic digital ulceration after receiving diltiazem SR 200 mg/day and thrice monthly iloprost infusions. Ten months later, antituberculosis chemotherapy was started and the steroid dosage reduced, after she developed a febrile illness with cough, pleuropericardial effusions, and sputum culture positive for tuberculosis (TB). Digital gangrene supervened in both hands and both feet despite daily intravenous iloprost infusions for 2 weeks. A day after starting sildenafil 50 mg three times a day her digital circulation and pain improved markedly; facial flushing was the only adverse reaction. In view of the slightly deteriorating digital ischaemia and experimental evidence,[2 3] we inferred that rifampicin treatment was inducing the metabolism of sildenafil. Its dosage was therefore doubled. Symptomatic improvement continued and ischaemic tissues became demarcated. However, 26 days after starting sildenafil she succumbed to uncontrolled pulmonary TB.

A 28 year old woman with scleroderma/lupus (case 2) who had been receiving diltiazem, domperidone, omeprazole, and penicillamine for about 4 years presented with progressive breathlessness. Computed tomography of the thorax suggested fibrosing alveolitis; prednisolone and azathioprine were started. Thereafter, she incurred occasional chest infections, other complications, and features of autoimmune diseases. She then developed persistent high grade fever, chills, rigors, night sweats, and increasingly severe digital arthralgia, vasculitis, and ischaemia. A polymerase chain reaction (PCR) of blood disclosed disseminated TB. Despite resolution of the sepsis after anti-TB chemotherapy, she developed progressive ischaemia and impending gangrene of her fingers, toes, and feet, despite regular infusions of iloprost for 2 weeks. One day after starting sildenafil 50 mg



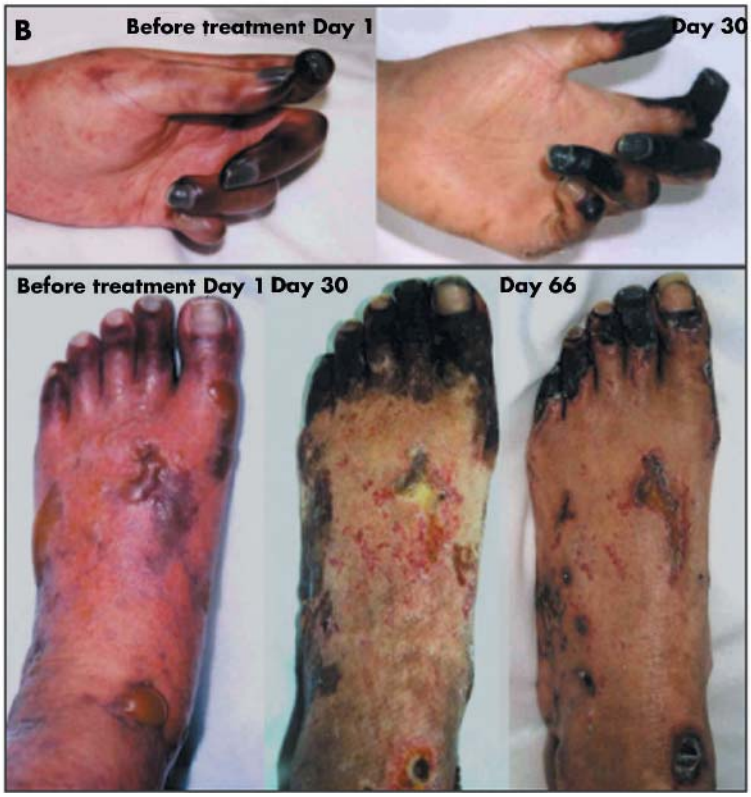




**Figure 1** (A), (B), and (C) refer to cases 1, 2, and 3, respectively. In all three cases, ischaemia of viable tissues resolved after treatment with sildenafil (and tadalafil in case 2). (B) shows that increased finger extension became possible after treatment.

three times a day, all four extremities showed marked symptomatic improvement, becoming warm, less painful, and less discoloured. Her digital vasculitis resolved; weeks later necrotic zones became demarcated and autoamputated. Owing to resurgence of active lupus, her prednisolone dosage was increased; her haematological/serological abnormalities regressed. After 48 days of sildenafil treatment, tadalafil (Cialis) 10 mg once daily was substituted for 78 more days, without any adverse reaction. Currently, the patient remains well and can stand.

A 76 year old woman with prior hypertension and ischaemic heart disease (case 3) presented with erythematous facial and finger rashes, myalgia, finger and toe ischaemic lesions, and proximal muscle weakness. Dermatomyositis and a disseminated malignancy were diagnosed. After mutually agreeing to stop further investigation, prednisolone treatment was started. Her digital ischaemia responded poorly to diltiazem SR and any improvement during iloprost infusions disappeared when they stopped. After 12 days and despite her past medical history, sildenafil treatment was cautiously started, with immediate reduction in peripheral pain and ischaemia and healing of toe ulcers. Although well tolerated, sildenafil was discontinued after 3 weeks, as the patient required treatment with nitrates.

## DISCUSSION

All three patients had immediate, subjective and objective improvements after initiating sildenafil, which was entirely consistent with Lichtenstein's observations, except that our patients were very severely afflicted.[4] In two patients, worsening RP and digital ischaemia appeared during active TB, consistent with the effects of sepsis.[5] Rifampicin, a powerful inducer of relevant P450 enzymes (apt to enhance sildenafil elimination[2 3]), appeared to affect their management. These

observations merit a randomised controlled trial to investigate the treatment of disabling RP with oral PDE-5 inhibitors.

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# Hereditary C1q deficiency and secondary Sjögren's syndrome

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A 13 year old Turkish boy with a known C1q deficiency and SLE-like disease developed recurrent parotitis. Investigations confirmed a secondary Sjögren's syndrome (SS). As far as we know, the association between C1q deficiency and SS has not been described before. The potential role of C1q in the pathogenesis of SS and systemic lupus erythematosus (SLE) might stimulate further research in understanding the pathogenesis of these and other autoimmune diseases. Screening patients with SS for complement deficiencies, including C1q deficiency, seems indicated.

Deficiency of the complement component C1q is a rare genetic disorder with susceptibility to recurrent infections with polysaccharide encapsulated micro-organisms and a high prevalence of autoimmune phenomena, most often SLE.

## CASE REPORT

At the age of 4 years a boy of consanguineous Turkish descent had meningitis of unknown origin. At the age of 8 years he presented with meningococcal sepsis and meningitis. In the late convalescent phase of this infection he developed arthritis of his right elbow and pericarditis. At the age of 10 years he was admitted owing to lobular pneumonia. Immunological studies at that time demonstrated no functional or antigenic activity of C1q based on a homozygous Glu-86 stop mutation in the C1qA gene exon 2. Both parents and a sibling sister were found to be asymptomatic heterozygous carriers. His sibling brother, who also developed SLE-like symptoms, was homozygous for this mutation.

At the age of 13 years the patient developed recurrent arthritis of the ankle and elbow. Two years later he presented with six episodes of alternate right and left parotitis. There were no complaints of dry mouth or dry eyes. Ultrasonography of the parotid gland during an episode of parotitis disclosed diffuse swelling. Salivary scintigraphy showed delayed tracer uptake. Ocular examination showed some corneal erosion, a normal Schirmer test, and a tear break up time of 10 seconds. A salivary gland biopsy showed lymphocytic sialoadenitis with a focus score of 4 and a percentage of plasma cells containing IgA of 9%, consistent with SS. Microscopic haematuria and proteinuria were not present. Immunological studies showed positive antinuclear antibodies (ANA), RNP antibodies, anti-Sm antibodies, anti-SSA antibodies, and a positive rheumatoid factor (RF). Anti-SSB antibodies and anti-dsDNA antibodies were not detected. A direct Coombs test and a serological test for syphilis were negative. Serum immunoglobulins were slightly raised. C3 and C4 were normal.

## DISCUSSION

In our patient a homozygous point mutation in the C1qA gene was demonstrated that has earlier been described in five families from the Slovak republic and Turkey.[1] With arthritis, a positive ANA test, and anti-Sm antibodies our patient has an SLE-like disease.[2] Patients with SLE commonly have sicca symptoms, which may be related to the concomitant occurrence of SS.[3] Secondary SS, in which the disease coexists with an autoimmune disease, is defined by the presence of either ocular or oral symptoms and two of four objective classification criteria.[4] Our patient with recurrent swollen salivary glands, autoantibodies to ANA, RF, and SSA, a salivary scintigraphy showing delayed uptake, and biopsy findings consistent with SS, meets the full criteria for secondary SS.

These observations suggest that absence or abnormal function of C1q leads to susceptibility for SLE and SS. This may be due to ineffective immune complex clearance that causes tissue injury, exposes autoantigens, and stimulates an autoantibody response.[5] In this respect it is significant that our patient had late onset reactive arthritis and pericarditis related to his meningococcal disease, which is also mediated by immune complexes.[6] Other data suggest a defective clearance of apoptotic cells, which promotes accumulation of nucleosomes (suggested antigens in SLE), which in turn drives an autoimmune response.[7]

In conclusion we report a patient with C1q deficiency, SLE-like disease, and secondary SS. This is the first time that an association between C1q deficiency and SS has been reported. It suggests a role for C1q in the pathogenesis of autoimmune diseases, possibly due to ineffective immune complex clearing or defective apoptosis, and warrants further research.

Screening of patients with C1q deficiency for SS, but especially screening of patients with SS for complement deficiencies, including C1q deficiency, seems indicated.

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