International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2010; **13:** e59–e61

CASE REPORT

Utilisation of plasma exchange in the treatment of digital infarcts in Wegener's granulomatosis

Albert LEUNG,[1,2] Chee B. SUNG,[3] Gargi KOTHARI,[4] Christopher MACK[3] and Christopher FONG[3]

[1]*Western Health,* [2]*St Vincent's Health,* [3]*Eastern Health, and* [4]*Melbourne Health, Melbourne, Victoria, Australia*

Abstract

Digital ischemia is a rare manifestation of Wegener's granulomatosis (WG) with previous management approaches based on the hypotheses of thromboembolic phenomenon and vasospasm. WG is an autoimmune, antineutrophil cytoplasmic antibody-predominant small-to-medium-vessel necrotising vasculitis which mainly affects the pulmonary–renal system. We report on a patient with WG presenting with digital infarction. We successfully treated this patient who had digital infarcts refractory to cyclophosphamide, steroids and vasodilator agents, with plasma exchange.

Key words: digital infarcts, plasma exchange, vasculitis, Wegener's granulomatosis.

INTRODUCTION

Wegener's granulomatosis (WG) affects 3 per 100 000 people with an average age of 55 years at presentation.[1] WG is classified into limited and classic, with limited WG predominantly involving the upper respiratory tract and has a better prognosis. Prior to the use of prednisolone and cyclophosphamide, 12-month mortality was as high as 80%.[2] Digital infarction is a rare presentation of WG in which various etiologies and management strategies have been prescribed.

CASE REPORT

We report on a case involving a 39-year-old married woman with no children who presented with multiple finger infarcts in the context of type 1 diabetes.

This patient initially presented to another hospital with a 2-day history of acute onset of painful purple discoloration of her left third and fourth finger digits. One week earlier, she was treated with oral antibiotics for a tooth abscess.

Her past history was notable for regularly reviewed type 1 diabetes complicated by diabetic nephropathy (glomerular filtration rate 53 mL/min/1.73 m^2, albumin-to-creatinine ratio 17.5 mg/mmol). She had no history of macrovascular complications. The patient also described a 15-year history of migratory small and large joint pains diagnosed as fibromyalgia. She had one prior miscarriage.

After transfer to our hospital for further evaluation and management, the patient developed hemoptysis and deteriorated in respiratory function, requiring non-invasive positive pressure ventilation.

Clinically, she had a gangrenous left fourth finger digit (Fig. 1). She was afebrile. Her peripheral pulses were present. Respiratory examination revealed bilateral crackles. No additional heart sounds were auscultated.

Initial investigations confirmed diffuse bilateral pulmonary infiltrates on chest X-ray and computed tomography pulmonary angiography (Fig. 2). There were no pulmonary emboli.

Her initial erythrocyte sedimentation rate was 71 mm/h and C-reactive protein was 207 mg/L. The

Correspondence: Dr. Christopher Fong, Consultant Rheumatologist, Department Head of Rheumatology, Box Hill Hospital, Nelson Road, Box Hill, Victoria 3128, Australia. Email: christopher.fong@easternhealth.org

Figure 1 Ischemic fourth digit with new ischemic areas on second and third digits.

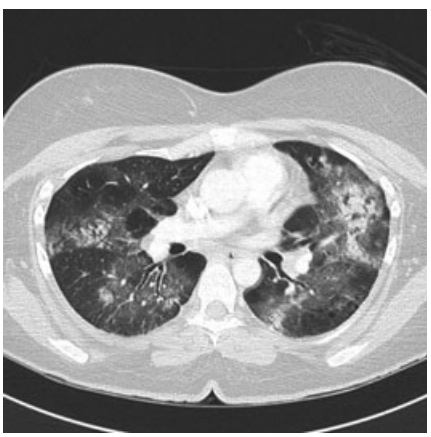

Figure 2 Computed tomography scan of the patient's lungs.

patient's hemoglobin was 97 g/L (mean cell volume 88 fL) with a platelet count of 524×10^9/L and a white cell count of 8.5×10^9/L.

An initial diagnosis of infective endocarditis was made and empirical antibiotics were commenced after blood cultures were taken. A transthoracic echocardiogram did not demonstrate any vegetations.

Further investigations revealed a proteinase 3–antineutrophil cytoplasmic antibody (c-ANCA) greater than 100 units/mL. A diagnosis of WG was made. Her renal evaluation did not show any active urinary sediments or dysmorphic red blood cells. Video-assisted thoracotomy (VAT) biopsy was done which revealed patchy nodular fibrotic changes with hemosiderin-laden macrophages. Widespread alveolar hemorrhage was noted. Further investigations included a negative antinuclear antibody, extractable nuclear antigen, double-stranded (ds)DNA, cryoglobulin, viral hepatitis and anti-phospholipid screen. Blood cultures were negative.

The patient was commenced on pulse methylprednisolone 1 g daily for 3 days followed by oral prednisolone 50 mg daily and cyclophosphamide 150 mg daily. Her respiratory function improved; however, her digital infarcts remained problematic despite the use of amlodipine 20 mg daily and environmental measures, with new areas of ischemia noted. Subsequently, she was given a treatment course of five plasma exchanges with improvement of the ischemic areas. Her left fourth gangrenous digit was surgically amputated and sent for histological analysis. There was vasculitis noted on histopathology with no thromboembolic phenomenon described.

DISCUSSION

Wegener's granulomatosis is an autoimmune, c-ANCA predominant small-to-medium-vessel necrotising vasculitis which mainly affects the pulmonary–renal system. Only 15% of patients with WG present with cutaneous manifestations. However, 50% will develop cutaneous manifestations during the course of the disease.[2] There are three categories of cutaneous manifestations: (i) palpable or non-palpable nodules due to small vessel vasculitis; (ii) subcutaneous nodes, ulcers and digital infarcts secondary to medium-vessel vasculitis; and (iii) polymorphic lesions such as rheumatoid nodules, pyoderma gangrenosum-like ulcers, urticaria, vesiculobullous lesions and gingival hyperplasia.[2] The prevalence of digital infarcts in WG is <1%.[3]

There have only been under a dozen case reports of digital ischemia in WG.[1,4–11] Review of these case reports suggests poor outcome with digital infarcts, often resulting in amputation of the affected area.[4] Onset of digital ischemia appears to be variable, ranging from the acute presentation to months after initial symptoms. This manifestation can occur despite immunosuppressive therapy.[1]

Different strategies have been employed to manage this rare and debilitating manifestation of WG. Management modalities have included: (i) general measures (e.g., avoiding cold, analgesia); (ii) immunosuppressant therapy such as cyclophosphamide, methylprednisolone; (iii) tumor necrosis factor-alpha (TNF-α) inhibitors such as infliximab, etanercept; (iv) monoclonal antibody (rituximab); (v) ANCA inhibition therapy such as intravenous immunoglobulin and plasma exchange; and (vi) vasodilator therapy (bosentan and iloprost). These therapies have had varying success.[2,12]

Review of other case reports revealed that some digital infarctions responded to cyclophosphamide and

steroid therapy.[1,4–9] A report by Avcin *et al.*[4] on a 12-year-old girl raised vasospasm as playing a role in digital ischemia. This patient had presented with hemoptysis, elevated c-ANCA (PR3-positive) WG and was treated with intravenous (i.v.) methylprednisolone and cyclophosphamide. Subsequently, she developed fluctuating episodes of purple discoloration of her digits. Treatment with nifedipine along with environmental measures (such as heat packs) controlled her digital symptoms.

In another report by Kejriwal *et al.*[1] a Maori woman with WG was treated with i.v. cyclophosphamide and prednisolone but later developed digital infarcts and gangrenous fingers, and was then treated with iloprost (prostaglandin analogue) infusion and further i.v. methyprednisolone and cyclophosphamide with stabilization of her symptoms.

In our patient, the interesting fact was that her initial symptoms were digital ischemia and pain with no other respiratory or renal involvement. Her recent dental procedure also made infective endocarditis a more likely diagnosis. It was not until the development of respiratory symptoms with radiographic changes and elevated ANCA levels that WG was thought to be the likely diagnosis. Despite treatment with immunosuppressive therapy, her digital ischemia continued to worsen resulting in amputation of her left 4th digit. Vasodilator treatment with amlodipine was also prescribed with minimal effect. Anticoagulation and thrombolysis was not applied due to her recent diffuse alveolar hemorrhage. She was given five courses of plasma exchange with good response.

Plasma exchange in theory, directly removes circulating ANCA and possibly also has benefit in extracting cytokines.[12] Plasma exchange has been primarily used in patients with severe renal disease and pulmonary hemorrhage with successful results.[13]

To the best of our knowledge, there have been no case reports on the use of plasma exchange to successfully treat digital infarcts. Other treatment modalities as mentioned above are primarily used to treat pulmonary and renal involvement of WG but not specifically for digital infarcts.[2] Why this patient responded to plasma exchange remains uncertain. Hypotheses could include immune complex deposition. A study by Hawke *et al.*[14] proposed that injury from vasculitic neuropathy arises from immune complex deposition diseases.

The outcome of digital ischemia tends to be poor in adults, often resulting in amputation. Various therapies have been employed to control digital ischemia associated with WG. Each presentation of WG-associated digital ischemia should be managed according to its merits and clinical context. In our case report, the use of plasma exchange was successful in controlling the patient's digital ischemia. Hence, in cases where digital ischemia secondary to WG is resistant to immunosuppressive therapy, plasmapheresis can be considered as an additional treatment option.

ACKNOWLEDGMENT

Professor Laurie McMahon, Head of Renal Medicine, Eastern Health, Victoria, Australia.

REFERENCES

1 Kejriwal R, Lim TM, Kumar S (2008) Wegener's granulomatosis and acute upper limb digital ischemia. *Int J Rheum Dis* **11**, 185–7.
2 Ko-Ren C, Carlson JA (2008) Clinical approach to cutaneous Vasculitis. *Am J Clin Dermatol* **9**, 71–92.
3 Andrew Carlson J, Chen K-R (2006) Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndrome. *Am J Clin Dermatol* **28**, 486–506.
4 Avcin T, Singh-Grewal D, Silverman ED, Schneider R (2007) Severe digital ischemia in a child with Wegener's granulomatosis. *Scand J Rheumatol* **36**, 178–80.
5 Bessias N, Moulakakis K, Lioupis C, *et al.* (2005) Wegener's granulomatosis presenting during pregnancy with acute limb ischemia. *J Vasc Surg* **42**, 800–4.
6 Handa R, Wali JP (1996) Wegener's granulomatosis with gangrene of toes. *Scand J Rheumatol* **25**, 103–4.
7 Binder C, Schattenkirchner M, Kruger K (1998) Severe toe gangrene as an early manifestation of Wegener granulomatosis in a young patient. *Z Rheumatol* **57**, 227–30.
8 Schmidt WA, Wernicke D, Kiefer E, Gromnica-Ihle E (2006) Colour duplex sonography of finger arteries in vasculitis and in systemic sclerosis. *Ann Rheum Dis* **65**, 265–7.
9 Modi M, Vats AK, Prabhakar S, *et al.* (2007) Acro-osteolysis and mononeuritis multiplex as a presenting symptom. *Indian J Med Sci* **61**, 212–5.
10 Karjalainen A, Hakala M (1996) Still another case of Wegener's granulomatosis with a digital ganere. *Scand J Rehumatol* **25**, 339.
11 La Civita L, Jeracitano G, Ferri C, Pedrinelli R, Dell'Omo G, Catapano G (1995) Wegener's granulomatosis of the elderly: a case report of uncommon severe gangrene of the feet. *Ann Rheum Dis* **54**, 328.
12 Lee RW, D'Cruz DP (2008) Novel therapies for anti-neutrohil cytoplasmic antibody associated vasculitis. *Drugs* **68**, 747–70.
13 Buhaescu I, Covic A, Levy J (2005) Systemic vasculitis: still a challenging disease. *Am J Kidney Dis* **46**, 173–85.
14 Hawke SH, Davies L, Pamphlett R, *et al.* (1991) Vasculitic neuropathy. A clinical and pathological study. *Brain* **114**, 2175.