

## Intravenous immunoglobulin therapy in vasculitic ulcers: a case of polyarteritis nodosa

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### Abstract

**Introduction** Polyarteritis nodosa (PAN) is a systemic necrotizing medium-size-vessel vasculitis with variable clinical manifestations. Diagnosis is confirmed by histology or angiography. The mainstay of treatment is corticosteroids alone or combined with cyclophosphamide (CYF).

**Case report** Seventy-one-year-old female, follow-up started in 1997 at the age of 56 for suspected relapsing febrile viral exanthema. Skin biopsy was performed and the diagnosis of lymphomatoid papulosis was made, with complete response to treatment with dapsone. In 2005, she presented with arthralgia, lower limb (LL) edema, livedo reticularis and elevated erythrocyte sedimentation rate (ESR). PAN was confirmed on histology and visceral angiography; antineutrophil cytoplasmic antibodies (ANCA) were negative. She responded to prednisolone but relapsed in 2006. Twelve cycles of CYF were administered, with clinical, angiographic and analytical improvement. In 2008, a new relapse occurred with LL neuropathic pain and ESR elevation. Electromyogram (EMG) confirmed axonal sensory polyneuropathy (PNP). Azathioprine was started with a poor response. A second EMG, 12 months later in 2009 still evidenced PNP, and nerve biopsy confirmed vasculitic neuropathy. In 2010, she had ulcers in LL and iron-deficient anemia. She started intravenous immunoglobulin (IVIG) for six cycles, achieving ulcer healing, absence of pain, no anemia and ESR normalization.

**Discussion** IVIG therapy has proven benefit in Kawasaki disease, also showing efficacy in refractory ANCA-associated vasculitis. In PAN, only very few case reports show benefit. In this case, IVIG therapy induced total remission of LL ulcers and PNP, suggesting that it may be useful in selected cases of refractory PAN.

**Keywords** IVIG · Vasculitic ulcers · Polyarteritis nodosa · Polyneuropathy

### Introduction

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that typically affects medium-sized vessels. It is primary in the majority of cases, but may also be secondary to viral infections for instance, mostly hepatitis B virus [1, 2].

It may present with several constitutional and organ-specific clinical manifestations but has a tendency to spare the lungs [1].

The diagnosis requires a high level of clinical suspicion due to its variable clinical manifestations and should be confirmed by histology or angiography. It is typically not associated with antineutrophil cytoplasmic antibodies (ANCA) [2–4].

The mainstay of treatment is corticosteroids either alone or combined with cyclophosphamide [5–8].

### Case report

A woman, born in 1941, with no previous relevant clinical conditions until the age of 56, initiated follow-up at the Dermatology Clinic in October 1997 for a suspected febrile viral exanthema. Viral serologies were negative for acute

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infection (Table 1). She improved with symptomatic treatment and topical therapy. However, symptoms relapsed and a skin biopsy was performed, suggesting the diagnosis of lymphomatoid papulosis. Treatment with dapsone was then started with complete remission.

In January 2005, she presented with livedo reticularis, cutaneous nodules, lower limb edema, fever and arthralgias. Erythrocyte sedimentation rate (ESR) was elevated (100 mm/h) (Fig. 1). Autoantibodies, including p-ANCA and c-ANCA, were negative (Table 2). Lower limb arterial and venous Doppler were also normal. A new skin biopsy was then performed and showed non-granulomatous lymphocytic vasculitis. Abdominal angiography revealed microaneurysms very typical of PAN, thus confirming the diagnosis. She initiated treatment with prednisolone (40 mg/day) with good response.

In March 2006, symptoms relapsed while tapering prednisolone. She initiated follow-up at Autoimmune Disease Clinic and started treatment with intravenous cyclophosphamide (750 mg/m<sup>2</sup> monthly for 6 months and afterwards every 3 months) completing 12 cycles (associated with prednisolone—60 mg/day initially, with further tapering reaching 10 mg/day). There was clinical improvement and normalization of ESR. She also repeated abdominal angiography by the end of treatment which was then normal.

In September 2008, a new cutaneous relapse occurred, associated with neuropathic pain in lower limbs. ESR was once again elevated. Electromyogram (EMG) revealed axonal sensitive polyneuropathy. She initiated treatment with azathioprine (0.9 mg/kg/day initially, increasing progressively until 2.7 mg/kg/day), maintaining prednisolone simultaneously. There was only a mild improvement. By 2009, symptoms persisted and ESR was increasing. The EMG still showed axonal sensitive polyneuropathy, without any improvement. Therefore, a nerve biopsy was performed that confirmed the vasculitic nature of neuropathy.

In September 2010, she presented with ulcers in lower limbs (Fig. 2a). ESR was still rising and she developed an iron-deficient anemia, gastroscopy and colonoscopy were both normal. In November 2010, she started treatment with intravenous immunoglobulin (IVIg) completing six cycles (2 g/kg in each cycle), while maintaining treatment with prednisolone and azathioprine (150 mg/day). There was clinical improvement after the second cycle (Fig. 2b), achieving, by the end of treatment (May 2011), complete ulcer healing, absence of pain, no anemia and ESR normalization. In November 2011, she maintained remission (Fig. 2c) with normal hemoglobin and ESR; at her last

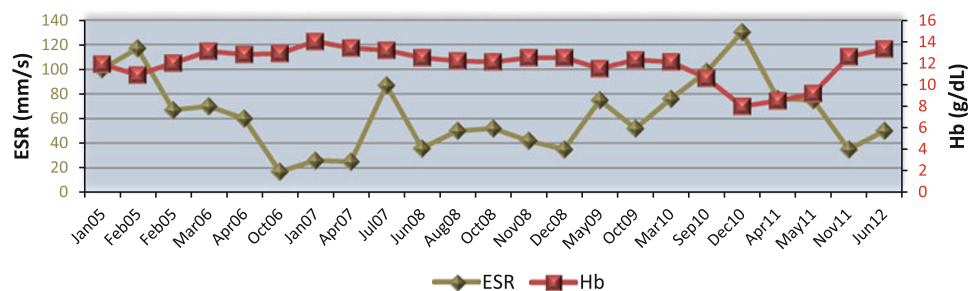
**Table 1** Viral serologies in October 1997

Hepatitis B virus	Negative
Hepatitis C virus	Negative
Mono test	Negative
Epstein Barr virus	IgG+
Cytomegalovirus	Negative
Herpes Simplex virus 1 and 2	IgG+
Parvovirus B19	IgG+
Echovirus	IgG+
Adenovirus	IgG+
Coxsackie A virus	Negative
Coxsackie B virus	IgG+

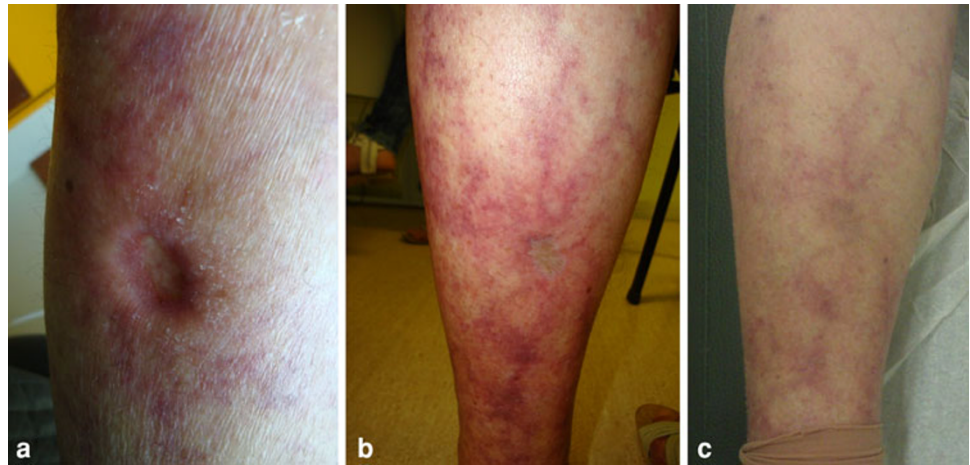
**Table 2** Autoimmunity testing results during follow-up

	2005	2008	2011	2012
c-ANCA	Negative	Negative	Negative	Negative
p-ANCA	Negative	Negative	Negative	Negative
ANA	Negative	Negative	Negative	Negative
Anti-dsDNA	Negative	Negative	Negative	
Anti-SSA		Negative	Negative	
Anti-SSB		Negative	Negative	
Anti-Sm			Negative	
Anti-RNP		Negative	Negative	
Anticardiolipin antibody	Negative	Negative	Negative	
Anti-B2GPI	Negative	Negative	Negative	
Circulating Immunocomplexes			Negative	
Anti-Rib-P		Negative	Negative	
Cryoglobulins			Negative	

**Fig. 1** Erythrocyte sedimentation rate (ESR) and hemoglobin (Hb) values since January 2005 until July 2012



**Fig. 2** Patient's lower limb in **a** September 2010, **b** January 2011 and **c** November 2011



appointment, in June 2012, she was still in clinical remission despite a small rise in ESR (treated with azathioprine 150 mg/day, without prednisolone since December 2011). Autoantibodies, including p-ANCA and c-ANCA, were tested once again in 2012, and were negative.

## Discussion

IVIG is a therapy with a complex mode of action which is not yet fully understood. It was initially used as replacement therapy in primary and secondary immunodeficiencies. More recently its use has been extended to several other clinical conditions such as infectious diseases, neuroimmunological diseases and systemic autoimmune diseases [9].

In particular, IVIG has shown benefit in several types of vasculitis.

There is evidence for IVIG use in Kawasaki disease [10, 11], suggesting a significant reduction in new coronary artery aneurysms. The benefit of IVIG in antineutrophil cytoplasmic antibody-associated vasculitis has been shown in one placebo-controlled [12] and in several open-label studies [13–24]. Most of those studies demonstrated a reduction in disease activity after failure of standard therapy with corticosteroids and immunosuppressants in patients with Wegener's granulomatosis or microscopic polyangiitis. In other vasculitis, evidence of benefit is limited to isolated case reports [9].

In PAN there are, to our knowledge, only 14 cases [25–36] in the literature showing benefit of IVIG, although sometimes only temporary [25–27]. Among those 13 cases, 4 [28–31] were children, 2 were Parvovirus B19-associated PAN [32] and 1 [33] Hepatitis B-associated PAN. Only one of those case reports was ulcer healing as in the case described above [34].

There are also case reports illustrating benefit of IVIG, particularly in vasculitic peripheral neuropathy in several

clinical conditions unresponsive to conventional treatment [37–40].

In the case described we present a patient with the diagnosis of PAN confirmed by visceral angiography which showed microaneurysms that are very typical features of PAN. Repeated ANCA negativity also supports this diagnosis and, together with the absence of renal or lung involvement, makes the alternate diagnosis of microscopic polyangiitis less likely at the moment.

The choice of treatment with intravenous immunoglobulin in this patient was based mainly on the failure of conventional treatment along with the presence of polyneuropathy of documented vasculitic nature [37–40]. The lower limb ulcers were also assumed to be secondary to vasculitis. The treatment resulted in total remission of all clinical and analytical manifestations, including not only absence of previously debilitating neuropathic pain but also ulcer healing. The iron-deficient anemia was also completely normalized, posing the hypothesis, it could be related with PAN as well.

At her last appointment she was still without any symptom, despite a new small rise in ESR, so there has been no relapse so far.

The case presented illustrates IVIG may be beneficial in selected cases of refractory PAN, including those presenting with vasculitic ulcers.

**Conflict of interest** Petra M. Pego, Inês Aguiar Câmara, José Pedro Andrade, João Matos Costa declare that they have no conflict of interest.

**Informed Consent** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

**Animal studies** No animal studies were carried out by the authors for this article.

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