

Single Case

Refractory Cutaneous IgA Vasculitis Treated with Omega-3 Fatty Acids

Maria A. Barnadas^a Montserrat M. Díaz Encarnación^b

^aDepartment of Dermatology, Hospital Santa Creu i Sant Pau, Barcelona, Spain;

^bDepartment of Nephrology, Fundació Puigvert, Barcelona, Spain

Keywords

IgA vasculitis · Omega-3 fatty acids

Abstract

Background: Omega-3 fatty acids (O3FA) have been used to treat IgA nephropathy (IgAN) but not cutaneous IgA vasculitis (IgAV). **Case Report:** A 47-year-old female was referred for cutaneous vasculitis. She had a 24-year history of flares of palpable purpura, arthralgia associated with hematuria, and proteinuria. We diagnosed cutaneous IgAV associated with IgAN. We administered prednisone at doses ranging from 10 to 45 mg/day to control the flares. To reduce prednisone exposure, different therapeutic strategies (colchicine, diphenhydramine, hydroxyzine, azathioprine, benzathine penicillin, and mycophenolate mofetil) were applied without success. After 11 years, therapy with O3FA capsules containing 460 mg eicosapentaenoic acid and 380 mg of docosahexaenoic acid t.i.d. was introduced, allowing the prednisone to be stopped 2 years later. When the dose of O3FA was decreased to 1 capsule on alternate days, the cutaneous flares reappeared, but they were again controlled when the patient took 1 O3FA capsule daily. **Conclusions:** O3FA can be useful to control cutaneous IgAV.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Introduction

According to the revised nomenclature, IgA vasculitis (IgAV), formerly Henoch-Schönlein purpura, is a small vessel vasculitis with IgA1-dominant immune deposits. IgAV affects the skin and the gastrointestinal tract and frequently causes arthritis [1]. As occurs in other vasculitides, IgAV can present with single-organ involvement [1]. Renal involvement indistinguishable from IgA nephropathy (IgAN) has been reported in 30–80% of patients with IgAV, resulting in renal failure in 11–38% of cases in long-term follow-up [2]. A subset of patients with IgAV therefore requires aggressive immunosuppressive therapy such as corticosteroids, azathioprine, cyclophosphamide, and mofetil mycophenolate [2, 3].

We present a patient diagnosed with cutaneous IgAV with IgAN who presented recurrent flares of extensive cutaneous vasculitis, without response to multiple immunosuppressive drugs. The disorder was well-controlled with omega-3 fatty acids (O3FA).

Case Report

A 47-year-old female with a history of asthma, hysterectomy, obesity, arterial hypertension, urinary tract infections, hypertriglyceridemia, and lumbar vertebra infarct was referred to our department in 1998 for cutaneous vasculitis.

Since the age of 23 years, she had had frequent flares of palpable purpura on the lower legs, with occasional arthralgia of the metacarpophalangeal joints, elbows, and knees, associated with hematuria and proteinuria. The flares were triggered by bronchitis episodes and bipedalism. On several occasions, they also appeared after urinary tract infections. Variable doses of prednisone were required to manage the flares.

In November 1998, the patient was admitted to the nephrology department. A kidney biopsy revealed mesangial proliferation with IgA deposits, and IgAN was diagnosed. She was referred to the dermatology department because of a palpable purpura flare on the lower legs. A biopsy of a lesion showed a perivascular inflammatory infiltrate composed of neutrophils with leukocytoclasia, extravasated red cells, and fibrin deposit in the vessel walls, consistent with the diagnosis of leukocytoclastic vasculitis (Fig. 1). A direct immunofluorescence study performed on involved and perilesional skin revealed IgA, C3, and fibrinogen in the walls of the skin vessels (Fig. 2). No other immunoglobulins were detected.

A laboratory test in November 1998 revealed urine protein 0.42 g/24 h and 2–3 red blood cells per high power field. Speckled antinuclear antibodies were positive at a titer 1/40, and the anti-DNA antibodies were negative. The level of IgA was 449 mg/100 mL (normal value 69–382). Hemoglobin, leukocytes, liver and kidney function tests, antiphospholipid, antistreptolysin, anti-HBV, anti-HCV, levels of IgG, IgM, rheumatoid factor, complement CH50, C3, C4 cryoglobulins, and antineutrophil cytoplasmic antibodies were all within normal range or negative.

After the diagnosis of IgAV was made, the patient presented frequent flares of cutaneous vasculitis. These flares were treated with prednisone at different doses and for variable time periods. We attempted to lower the dose of prednisone by administering azathioprine, colchicine, diphenhydramine, hydroxyzine, and benzathine penicillin, but none of these treatments showed any efficacy to control flares.

In 2002, IgA levels were 769 mg/100 mL (normal value 69–382) and IgAκ monoclonal gammopathy was detected. Bence-Jones urine protein test was negative. The patient was referred to the hematology department. No further treatment was required.

In June 2004, she presented several flares of widespread cutaneous vasculitis involving the lower legs, abdomen, and arms. Several courses of oral prednisone were administered at a maximal dose of 45 mg/day. In January 2008, kidney function tests were normal. However, in view of the persistent flares of extensive cutaneous lesions, mycophenolate mofetil 360 mg b.i.d. was initiated to reduce prednisone exposure. No improvement was observed, and a dose of prednisone 20 mg every 2 days was maintained.

In January 2009, therapy with O3FA capsules containing 460 mg eicosapentaenoic acid and 380 mg of docosahexaenoic acid t.i.d. was added to the oral corticotherapy due to the persistence of cutaneous activity. The flares diminished in frequency and intensity, allowing prednisone to be tapered down and stopped in January 2011. O3FA was also slowly tapered down to 1 capsule every 2 days. However, in May 2012, a cutaneous flare again appeared on the legs, and the O3FA dose was increased to 1 capsule per day. In July 2012, a new flare of vasculitis appeared on the lower legs (Fig. 3) and abdomen, disappearing after increasing the O3FA dose to 1 capsule 3 times a day. This dose was tapered down to 1 capsule a day in November 2012. The patient has continued to take this same dose of O3FA daily and has been free of flares to date. The most recent laboratory tests, in October 2015, included IgA level, antinuclear antibodies, and urine analysis; all were within the normal range.

Discussion

We present an adult patient who presented IgAV with renal and skin involvement. The kidney lesion responded to corticosteroid therapy, but the cutaneous flares were refractory to immunosuppressants, and oral corticosteroids were required. The administration of O3FA allowed the dose of prednisone to be tapered off. We are not aware of any previous report of IgAV treated with O3FA.

We consider that O3FA contributed to the control of skin lesions for 2 reasons. First, after O3FA was introduced, the flares of palpable purpura decreased in frequency and intensity, allowing suppression of corticosteroids. Second, there was a relationship between the dose of O3FA and disease activity. When the dose was tapered to 1 capsule every 2 days, new lesions of palpable purpura appeared, but when the dose was again increased the lesions improved.

The rationale to treat this patient with O3FA is that kidney lesions associated with IgAV are indistinguishable from IgAN, which has been treated with O3FA before [4, 5]. We have to consider that, when therapy with O3FA was started, kidney function was normal and neither proteinuria nor hematuria was detected, probably due to previous prednisone therapy.

The efficacy of O3FA in IgAN is controversial. In 1994, Donadio et al. [6] observed that patients given O3FA showed a 2-year delay in the rate at which renal function was lost, but Hogg et al. [7] were unable to demonstrate the superiority of either prednisone or O3FA over placebo to slow progression of renal disease. In a post hoc analysis, however, Hogg et al. [8] observed that the efficacy of O3FA on proteinuria in pediatric and adult patients with IgAN was associated with a dose-dependent effect on plasma phospholipid eicosapentaenoic and docosahexaenoic acid. Nevertheless, Donadio et al. [9] did not find that efficacy of O3FA was dose dependent on the basis of body size.

The authors of two recently published meta-analyses agreed that there are insufficient data to confirm the efficacy of O3FA in improving renal function in IgAN [4, 5]. With respect to proteinuria, the conclusions were inconsistent. Liu et al. [5] did not find any significant reductions in proteinuria, but Chou et al. [4] did, independently of the dose used. They at-

tributed this discrepancy to the fact that they included post hoc, unpublished data making the effect of the therapy more evident and reliable. Other authors state that O3FA should be considered in progressive IgAN, and they emphasize that well-designed, adequately powered, randomized, controlled clinical trials are needed to assess the potential benefits of O3FA on the prognosis of kidney disease and patient survival [10].

Various mechanisms of O3FA action have been suggested. In rats, O3FA was shown to improve endothelial function and to have anti-inflammatory and anti-thrombotic effects. It was also seen to decrease plasma triglycerides and very low-density lipoprotein and to slightly increase low-density lipoprotein, without any changes in high-density lipoprotein and total cholesterol [10]. In addition, it was proposed that O3FA influences immune function in vivo by attenuating mediator production, leukocyte homing, delayed hypersensitivity, allograft rejection, and acute inflammatory responses in animal models of human inflammation and autoimmune disease. Both eicosanoid-dependent and eicosanoid-independent pathways appear to mediate these effects [11]. O3FA decreases TNF α -stimulated MCP1 transcription through the ERK-NF- κ B pathway in renal mesangial cells [12]. Furthermore, in salt-sensitive hypertensive rats it inhibits renal damage, decreasing TNF α -NF- κ B pathway activation and monocyte recruitment in vivo. These data, and data from other authors, support the position that O3FA has anti-inflammatory properties that offer potential benefits in some inflammatory diseases [13].

We consider that O3FA is an alternative, less iatrogenic therapy than immunosuppressive drugs such as corticosteroids, azathioprine, and cyclophosphamide for patients with steroid-refractory cutaneous IgAV. Although most patients do not require immunosuppressive therapy, some need such treatment for long periods. Because our patient did not present kidney involvement when therapy with O3FA was started, we do not know whether this therapy had any influence in kidney function. The benefits of O3FA therapy seen in our patient, however, suggest that it can be useful to treat patients with recurrent cutaneous IgAV. Prospective studies are needed to evaluate its efficacy in the treatment of cutaneous IgAV.

Acknowledgments

We would like to thank Mrs. Carolyn Newey for editing the manuscript.

Statement of Ethics

The patient reported here gave informed consent for the therapy.

Disclosure Statement

We declare that we have no conflicts of interest.

References

- 1 Jennette JC, Falc RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al: 21012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.
- 2 Han F, Chen LL, Ren PP, Le JY, Choong PJ, Wang HJ, Xu Y, Chen JH: Mycophenolate mofetil plus prednisone for inducing remission of Henoch-Schönlein purpura nephritis: a retrospective study. *J Zheijiang Univ Sci B* 2015;16:772–779.
- 3 Tanaka Y, Nakashima Y, Mima T, Ohya M, Yamamoto S, Kobayashi S, Masumoto A, Masumoto K, Yano T, Moribata M, Yoshimoto W, Yamanaka S, Koreeda D, Hanba Y, Tatsuta K, Sakaguchi T, Negi S, Shigematsu T: Effects of cyclophosphamide pulse therapy on the clinical and histopathological findings, particularly crescent formation, in a patient with adult-onset steroid-refractory Henoch-Schönlein purpura nephritis. *Int Med* 2015;54:2207–2211.
- 4 Chou HH, Chiou YY, Hung PH, Chiang PC, Wang ST: Omega-3 fatty acids ameliorate proteinuria but not renal function in IgA nephropathy: a meta-analysis of randomized controlled trials. *Nephron Clin Pract* 2012;121:c30–c35.
- 5 Liu LL, Wang LN: Omega-3 fatty acids for IgA nephropathy: a meta-analysis of randomized controlled trials. *Clin Nephrol* 2012;77:119–125.
- 6 Donadio JV, Bergstralh EJ, Offord KP, Spencer DC, Holley KE; Mayo Nephrology Collaborative Group: A controlled trial of fish oil in IgA nephropathy. *N Engl J Med* 1994;331:1194–1199.
- 7 Hogg RJ, Lee J, Nardelli N, Julian BA, Cattran D, Waldo B, Wyatt R, Jennette JC, Sibley R, Hyland K, Fitzgibbons L, Hirschman G, Donadio J, Holub BJ: Clinical trials to evaluate omega-3 fatty acid and alternate day prednisone in patients with IgA nephropathy: report from the southwest pediatric nephrology group. *Clin J Am Soc Nephrol* 2006;1:467–474.
- 8 Hogg RJ, Fitzgibbons L, Atkins C, Nardelli N, Curtis Bay R: Efficacy of omega-3 fatty acids in children and adults with IgA nephropathy is dosage- and size-dependent. *Clin J Am Soc Nephrol* 2006;1:1167–1172.
- 9 Donadio JV, Bergstralh EJ, Bibus DM, Grande JP: Is body size a biomarker for optimizing dosing of omega-3 polyunsaturated fatty acids in the treatment of patients with IgA nephropathy? *Clin J Am Soc Nephrol* 2006;1:933–939.
- 10 Fassett RG, Gobe GC, Peake JM, Coombes JS: Omega-3 polyunsaturated fatty acids in the treatment of kidney disease. *Am J Kidney Dis* 2010;56:728–742.
- 11 Petska JJ: N-3 polyunsaturated fatty acids and autoimmune-mediated glomerulonephritis. *Prostaglandins Leukot Essent Fatty Acids* 2010;82:251–258.
- 12 Diaz Encarnacion MM, Warner GM, Cheng J, Gray CE, Nath KA, Grande JP: n-3 fatty acids block TNF- α -stimulated MCP-1 expression in rat mesangial cells. *Am J Physiol Renal Physiol* 2011;300:F1142–F1151.
- 13 Diaz Encarnacion MM, Warner GM, Gray CE, Cheng J, Keryakos HK, Nath KA, Grande JP: Signaling pathways modulated by fish oil in salt-sensitive hypertension. *Am J Physiol Renal Physiol* 2008;294:F1323–F1356.

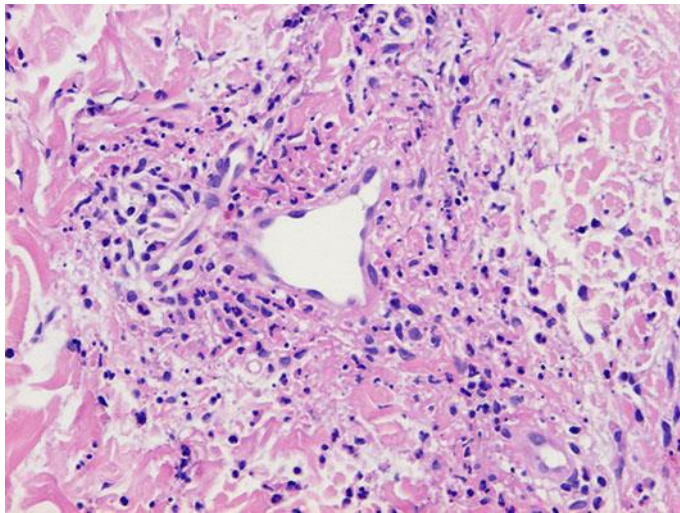


Fig. 1. Histopathological findings of the skin biopsy showing a perivascular inflammatory infiltrate composed of neutrophils, with leukocytoclasia, extravasated red blood cells, and fibrin around blood vessels. HE. $\times 200$.

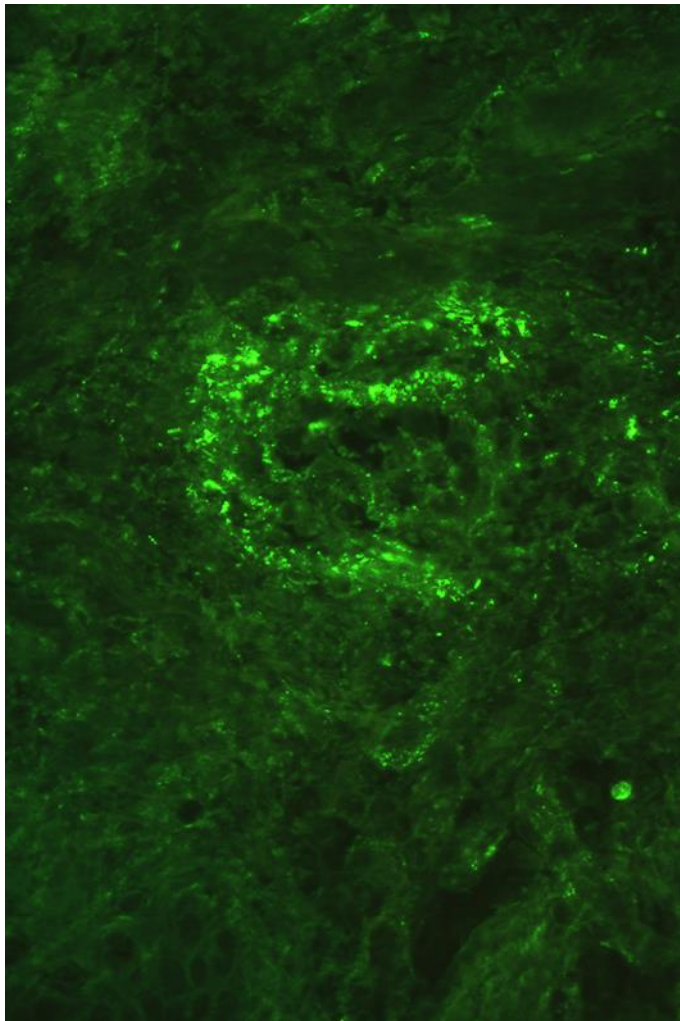


Fig. 2. Direct immunofluorescence of a purpuric lesion showing IgA in the vessel walls.



Fig. 3. Clinical aspect of the flare of cutaneous vasculitis on the leg in July 2012.