Unusually indolent MPO-ANCA: associated vasculitis—report of two cases

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Received: 23 July 2012 / Accepted: 17 October 2012 / Published online: 7 February 2013
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Abstract Vasculitis associated with antineutrophil cytoplasmic antibodies specific to myeloperoxidase generally presents as a life- and organ-threatening disease that evolves over several months. It is a syndrome in which prompt diagnosis and therapy are important both in terms of short-term survival and long-term organ damage. Two cases with quite a different course, sustained and indolent with limited progression over many years, are described in this report. They are compared to cases in the literature. Indolent cases of granulomatous polyangiitis associated with antineutrophil cytoplasmic antibodies against proteinase-3 are well recognised, but these two cases of microscopic polyangiitis are almost unique.

Keywords Vasculitis · Antineutrophil cytoplasmic antibody · Indolent course

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is generally a life- and organ-threatening disease that evolves over several months. As such these conditions are syndromes that mandate prompt diagnosis and initiation of appropriate therapy. Indeed, there is evidence that a delay in making the diagnosis and starting therapy is associated with more damage and a poorer outcome. Indolent cases of granulomatous polyangiitis (GPA) are

well described, usually affecting organs such as the eyes, mouth, nose and other parts of the upper respiratory tract [1]. Such organ involvement is not immediately life threatening and, provided the disease does not spread to more vital organs such as the kidneys or lungs, the inflammation can grumble along for several years. Such an occurrence is not as common in microscopic polyangiitis (MPA), although cases without severe renal or pulmonary features have been reported [2, 3]. Non-life-or-organ-threatening disease can occur in MPA and indolent disease can potentially occur. Two such cases are described here.

Case report

Case 1: A 72-year-old female Caucasian. The current illness began in 1999 with a fairly rapid onset of motor and sensory symptoms in the right lower leg and foot. She was reviewed by a neurologist who diagnosed mononeuritis multiplex and ordered tests to diagnose a vasculitis. The results showed a positive ANA, titre 320(H), negative ENA and RF, normal complement studies—C3 and C4 and a positive pANCA titre 160. A thorough clinical examination and extensive investigations found no evidence of any other organ involvement and the neurological symptoms resolved spontaneously over an 8-week period. The pros and cons of initiating any immunosuppressive therapy were discussed and mutually decided against. Four years previously the patient had had diplopia attributed to a trochlear nerve palsy, which recovered spontaneously over 6 months. Since then the patient has had seven further episodes of peripheral neuropathy, all affecting the lower limbs, sometimes the left foot, sometimes the right and once both. Recovery has always been spontaneous. When last reviewed the sensory examination was normal, but

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motor testing showed some minor residual weakness of dorsiflexion on the right. Repeated thorough clinical examinations and laboratory tests showed no other organ involvement. Throughout the patient has manifested a low positive MPO-ANCA during symptomatic periods, tending to become negative when well. Despite urging the patient has again declined any specific therapy.

Case 2: A 37-year-old male Caucasian. The current illness began in 1996 with recurrent episodes of severe migratory arthralgia and painful palpable 1-cm sub-cutaneous nodules. Occasionally a joint would swell for a few days. The frequency of these episodes waxed and waned, but they increased in 2001 and he was referred for review. Thorough clinical examination and investigation revealed no other organ involvement, and a decision was taken to carefully monitor the patient for further developments, particularly pulmonary and renal. He had had manifest type 1 diabetes since 1994 and was under close review anyway. The pANCA pattern was again detected by immunofluorescence, MPO-ANCA by ELISA, ANA was positive, titre 320(S), RF was just elevated at 23 KIU/l ($N < 20$), cryoglobulins were not detected, Hep B and C serology was negative, and complement levels—C3 and C4 were normal. The symptoms recurred intermittently over the next few years; the MPO-ANCA remained significantly elevated but there was no progression. Nine years later in 2010 he reported that the episodes were increasing in frequency, the number of joints, skin lesions and severity. He was seen in a peripheral hospital with chest pain and after ECG a diagnosis of pericarditis was made. He had no pulmonary or renal manifestations. Urinary sediment and creatinine levels have stayed normal. He attended for review and a decision was made to commence oral methotrexate (MTX) as a single agent as has been reported for limited disease previously [4] because the recurring symptoms were interfering with his life and especially work as a long-haul truck driver and farmer. Prednisone was specifically avoided because of his type 1 diabetes. The condition was very indolent and it was felt that a slow remission induction would be satisfactory. The MTX was commenced in March 2011 and escalated up to 20 mg/week. Soon after starting he reported no more skin or joint problems. When mouth ulcers occurred the dose was initially dropped to 10 mg/week. He developed a hot swollen knee joint and had another episode of chest pain identical to the previous one. Both resolved and he is now asymptomatic on MTX 17.5 mg/week. The MPO-ANCA titre initially rose, but is now beginning to fall. No other features have developed.

The measurement of pANCA was by immunofluorescent microscopy (Euroimmun Granulocyte Mosaic, Lubeck, Germany) and the PR3 and MPO-ANCA by ELISA (Organtec, Mainz, Germany). They are shown in

two figures together with results of C reactive protein and Birmingham vasculitis activity score (BVAS) version 3 [5]. Neither patient was ever PR3-ANCA positive.

Results

The results are shown in Figs. 1 and 2. It can be seen that the CRP was only occasionally elevated and the BVAS, although paralleling the MPO-ANCA, was not especially high, emphasising the dearth of major organ involvement.

Discussion

These two patients are presented as interesting examples of indolent disease associated with MPO-ANCA. A presumptive diagnosis was made in each as there is no histopathological confirmation of the presence of small-vessel vasculitis. The original definition of MPA does not mandate the presence of renal and/or pulmonary features [6]. Indeed, peripheral neuropathy is seen in about 60 % of patients with MPA, arthralgias in about 50–60 % and vasculitis including skin nodules in about 60–70 %. The clinical features exhibited here are at least consistent with the minor clinical features of MPA. Pericarditis is seen in about a third of MPA patients, so this feature too is consistent with such a diagnosis [2, 3]. In both of those case series indolent disease was measured in months, not years, with the exception of a patient in Savage's series [2] with a 10-year prodrome.

Case 1 manifests recurrent episodes of peripheral neuropathy, which has been accompanied by objective motor and sensory signs. Spontaneous recovery has occurred, recently with a suggestion of mild permanent damage.

Fig. 1 The MPO-ANCA, CRP and BVAS are plotted over the period of time that this patient has been under observation. MPO-ANCA is measured in units/ml, CRP in mg/l; BVAS is a numeric score

Fig. 2 The MPO-ANCA, CRP and BVAS are plotted over the period of time that this patient has been under observation. MPO-ANCA is measured in units/ml, CRP in mg/l; BVAS is a numeric score

The p-ANCA and MPO-ANCA levels have been relatively low to date, but definite and generally fluctuating with the clinical activity.

Case 2 has more dramatic features and a much higher level of MPO-ANCA. The high level has been sustained for many years and is only now beginning to come down with MTX therapy. The level of MPO-ANCA overlaps with the levels we see in our department for definite cases of MPA.

Despite the passage of many years, neither patient has ever shown any evidence of renal or pulmonary disease. In general it is not well understood why multisystem

autoimmune diseases target one particular organ system, why these patients have not progressed or indeed why those that do progress do so; this can currently only be guessed at. It has been clear for some time that there are very indolent cases of GPA and these two cases suggest that the same phenomenon can be observed in MPA.

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