Microscopic polyangiitis (microscopic polyarteritis) with late emergence of generalised Wegener's granulomatosis

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Abstract

Objectives—Recent proposals for the nomenclature of systemic vasculitis have focused on a distinction between (classic) polyarteritis nodosa (PAN) and microscopic polyangiitis or polyarteritis (MPA). Thus, MPA may cause necrotising vasculitis of medium sized or small arteries but, unlike PAN, involvement of “microscopic” vessels must always be present in the former. This study aimed to show that the term “MPA” may represent a source of misinterpretation and to help illustrate difficulties of applying diagnostic criteria/definitions for conditions of unknown aetiology or variable clinical presentation and course.

Methods—Among 1250 consecutive patients screened for antineutrophil cytoplasmic antibodies (ANCA), 59 had been found to have idiopathic necrotising and crescentic glomerulonephritis plus ANCA while five had been found to have isolated pulmonary haemorrhage with biopsy verified necrotising alveolar capillaritis plus ANCA. None of these patients had clinical or histological evidence of Wegener's granulomatosis (WG) or evidence of biopsy verified vasculitis involving vessels other than glomerular or pulmonary capillaries at the time of presentation.

Results—Six of the 64 patients who met definition criteria for MPA at the time of initial diagnoses had entered into complete clinical remission upon appropriate corticosteroid and cyclophosphamide treatment between two weeks and three months, though subsequently (20 to 72 months; mean time: 42.3 months) developed characteristic clinical and histological features of overt WG.

Conclusions—Microscopic polyangiitis/polyarteritis may be a dynamic condition with clinical and histopathological features evolving over time to other forms of small vessel vasculitis, mainly WG, thereby meaning that follow up would be necessary not only to control a given patient but also to make a final diagnosis. This follow up should be for a long time as there may be a long interval between initial presentation and subsequent development of WG lesions.

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consensus on the names for some of the most common forms of systemic vasculitis and to construct root definitions for the vasculitides so named”.¹ For that reason, an ad hoc multidisciplinary committee was created, which was composed of clinicians and pathologists who had extensive experience with diagnosing systemic vasculitides. Unlike the American College of Rheumatology (ACR) Subcommittee on Classification of Vasculitis, a main goal of the Chapel Hill Consensus Conference (CHCC) was to develop “a standardized nomenclature system” rather “than determining the clinical criteria required to classify or diagnose individual patients as appropriate for one of the nomenclature categories”. Also, an important novelty adopted by the CHCC concerned the name and definition of (classic) polyarteritis nodosa (PAN) and microscopic polyangiitis or polyarteritis (MPA). The proposed distinguishing feature for PAN compared with MPA is the absence versus the presence of vasculitis in arterioles, venules, or capillaries. According to these definitions, although MPA may cause necrotising vasculitis of medium sized or small arteries, involvement of “microscopic” vessels must always be present. In contrast, (classic) PAN must have no involvement of “microscopic” vessels including no glomerulonephritis or pulmonary capillaritis. In summary, the name “MPA” implies a necrotising vasculitis with few or no immune deposits (pauci-immune), involving small vessels (that is, capillaries, venules, or arterioles). Also, necrotising arteritis involving small and medium sized arteries may be present, necrotising glomerulonephritis is very common, pulmonary capillaritis often occurs, and it is strongly associated with antineutrophil cytoplasmic antibody (ANCA) serum positivity.

In this report, I show that, in addition to these findings, MPA is not necessarily a static but a dynamic condition where clinical and histopathological features may evolve over time to other well recognised forms of systemic necrotising small vessel vasculitis, mainly Wegener's granulomatosis (WG).

Methods

Between 1987 to 1997, 1250 consecutive patients with different forms of systemic vasculitis, connective tissue diseases, and renal and pulmonary disorders were screened for ANCA to determine the prevalence and clinical value of these antibodies in these patients. Epidemiological, clinical, histological, treatment, and

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In 1994, the results of an international meeting were reported, its goals being “to reach

Table 1 Characteristics of the patients at the time of the first diagnosis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (y)/sex	47/F	58/F	32/M	67/F	26/M	38/F
Clinical features and diagnosis	Mild renal failure INCGN	Mild renal failure INCGN	Moderate renal failure + PH INCGN + NAC	Severe renal failure INCGN	Severe isolated PH NAC	Moderate renal failure INCGN
ANCA (specificity/titre)	PR3/1:1280	PR3/1:1280	MPO/1:5120	PR3/1:2560	MPO/1:1280	MPO/1:640
Time for remission	1 month	3 weeks	3 months	2 weeks	2 months	1 month
Latent period*	36 months	20 months	72 months	42 months	48 months	36 months
Recrudescence in latent period	None	None	None	None	None	None
Length of time on treatment	36 months	20 months	24 months	24 months	18 months	30 months
Last control†	3 weeks	1 month	3 months	2 months	2 months	6 weeks
Treatment‡	Low dose cyclophosphamide	Low dose corticosteroids + cyclophosphamide	None	None	None	None

*Until development of Wegener's granulomatosis (WG); †before development of WG; ‡at the time of development of WG. INCGN: idiopathic necrotising and crescentic glomerulonephritis; PH: pulmonary haemorrhage; NAC: necrotising alveolar capillaritis; ANCA: antineutrophil cytoplasmic antibodies; PR3: proteinase 3; MPO: myeloperoxidase.

follow up data from each patient were registered and tabulated in appropriate standardised questionnaires. ANCA were tested by means of both indirect immunofluorescence (IIF) on ethanol fixed neutrophils and enzyme linked immunosorbent assays using myeloperoxidase (MPO) and proteinase 3 (PR3) as a substrate.² Sixty eight patients with pauci-immune idiopathic necrotising and crescentic glomerulonephritis (INCGN) and five with isolated pulmonary haemorrhage (IPH) who had pauci-immune necrotising alveolar capillaritis (NAC) as underlying histopathological substrate were seen among all 1250 patients. Definitions of both INCGN and NAC have been reported elsewhere.^{2,3} Of note, none of these 73 patients had evidence of biopsy verified vasculitis involving vessels other than glomerular or pulmonary capillaries or evidence of granulomas at the time of presentation. Also, none of these 73 patients had clinical suspicion of WG or evidence of any clinical involvement of other systems through careful physical examination and several investigations including ear, nose, and throat examination, sinus radiographs and computed tomography evaluation of cranial structures. ANCA were detected in 126 of the total series of 1250 patients (87 with MPO-ANCA and 39 with PR3-ANCA). In addition, these antibodies were found in 59 patients with INCGN (52 with MPO-ANCA and seven with PR3-ANCA) and in all five with IPH (MPO-ANCA in four and PR3-ANCA in one).

Interestingly, 11 patients with INCGN developed pulmonary haemorrhage concurrently (pulmonary-renal syndrome); a lung biopsy was performed in six and pauci-immune NAC without vessel involvement other than that of pulmonary capillaries was found in five cases (four with MPO-ANCA and one with PR3-ANCA).

Results

To date, five of the 68 (7.4%) patients with INCGN (three with PR3-ANCA and two with MPO-ANCA) and one of the five with IPH (who had MPO-ANCA) have developed clinically overt WG (table 1).

All six patients with late emergence of WG had characteristic histopathological findings in lungs (cases 1, 2 and 3), nasal mucosa (case 4), soft palate (case 5), and endobronchial (case 6) biopsies. Table 2 summarises the clinical features at the time of developing WG. At the time of an initial diagnosis of INCGN, all five patients with this disorder had mild to severe renal failure, with one of them (case 3) having simultaneous pulmonary haemorrhage (with lung biopsy compatible with NAC) (table 1). Furthermore, these five patients had entered into clinical remission with complete recovery of renal function, and disappearance of lung haemorrhage in case 3, upon appropriate corticosteroid and cytotoxic treatment. The remaining patient with an initial diagnosis of severe IPH (case 5) had also entered into remission, at that time, upon intensive corticosteroid and cyclophosphamide treatment. The time passed between the initial diagnoses of INCGN and IPH and the achievement of complete remission ranged from 14 days to 3 months (table 1). Definition of remission was based on both clinical and laboratory data, but no scoring system for disease activity was used. Tests of disease activity included ANCA, C reactive protein, and erythrocyte sedimentation rate. When all six patients had entered into remission, in addition to signs and resolution of symptoms (for example, recovery of renal function, disappearance of lung haemorrhage), they experienced a decrease in ANCA serum titres (with ANCA negativisation in some cases), C reactive protein and erythrocyte sedimentation rate. The latent period preceding

Table 2 Clinical features of the patients at the time of developing Wegener's granulomatosis

	Clinical features at relapse	Outcome after treatment
Case 1	Low grade fever, cough and haemoptysis, multiple pulmonary nodules, mild renal failure	Complete remission
Case 2	Cough, purulent nasal discharge, scleritis, multiple cavitated pulmonary nodules, moderate renal failure	Complete remission
Case 3	Dyspnea, haemoptysis, diffuse patchy alveolar infiltrates, lung haemorrhage, retro-orbital mass lesion	Complete remission
Case 4	Bloody nasal discharge with nasal mucosal ulceration, sinus inflammation, bilateral facial nerve palsy, orbital disease, mild renal failure	Complete remission
Case 5	Haemoptysis, diffuse patchy alveolar infiltrates, lung haemorrhage, sinus and oral inflammation, soft palate ulceronecrotising lesions, leucocytoclastic vasculitis	Dead
Case 6	Cough and haemoptysis with normal chest roentgenogram, endobronchial pseudotumoral lesion on bronchoscopy, serous otitis media, moderate renal failure	Complete remission

the appearance of diagnostic lesions of WG ranged between 20 months and 6 years, with a mean time of 42.3 months (table 1). It should be noted that, at the time of the initial diagnoses, none of these six patients had signs or symptoms suggestive of WG (such as ear, nose or throat manifestations) or of other vasculitic or connective tissue disorders. When these patients developed signs and symptoms of WG, they were previously (last control: three weeks to three months) symptom free, with ANCA being negative in three and at lower IIF serum titres, as compared with the time of initial diagnosis, in the other three. Moreover, at that time, four patients were not receiving any sort of treatment, one was receiving low dose corticosteroids and cyclophosphamide treatment, and one was receiving cyclophosphamide maintenance treatment. At the time of developing WG, in addition to the signs and symptoms described above, four patients with a previous diagnosis of INCGN had mild to moderate renal failure, the one patient with a former diagnosis of pulmonary-renal syndrome (case 3) had no renal failure now but a lung haemorrhage relapse developed, and the one patient with a former diagnosis of IPH (case 5) had a lung haemorrhage relapse (table 2). All six patients were given induction treatment with corticosteroids and cyclophosphamide, leading to complete responses in all but one who died from diffuse pulmonary haemorrhage and refractory respiratory failure (case 5) (table 2). Finally, all six patients had showed a new positivisation, or increase in serum titres, of ANCA when WG manifestations developed, yet maintaining the same antigenic specificities as formerly.

Discussion

In my opinion, the term MPA may represent a source of misinterpretation. According to the CHCC on the Nomenclature of Systemic Vasculitis,¹ MPA may cause a necrotising vasculitis of medium sized or small arteries, or both, which is histologically identical to that seen in (classic) PAN. I believe that this vasculitis classification has been a bone of contention in the “ANCA/vasculitis world” since its inception and I suspect that most clinicians are unhappy with the way PAN is treated. For instance, if we bear in mind the definition of its microscopic variant, then a given patient with pauci-immune INCGN without evidence of vasculitis in vessels other than glomerular capillaries has MPA. Also, a patient having IPH with pauci-immune NAC without granulomas or evidence of vasculitis in vessels other than pulmonary capillaries has MPA. Likewise, a patient with a combination of both conditions (that is, pulmonary-renal syndrome) without vessel involvement other than that of glomerular and pulmonary capillaries has MPA. Therefore, my six present cases would have been named and defined as MPA at the time of initial diagnoses, according to the CHCC. Furthermore, according to it, 19 previously reported patients presenting with severe INCGN, without any sort of extrarenal involvement, who showed a delayed onset (4 to 78 months) of generalised,

biopsy verified WG⁴ would have been named and defined as having MPA at the time of first onset; of importance, most of these patients were receiving long term dialysis when respiratory disease developed, thereby confirming that WG became active during chronic renal failure or dialysis. Finally, a recent firstly characterised subset of patients presenting with severe diffuse IPH with pauci-immune NAC in the absence of any clinical, serological, or histological evidence of an accompanying systemic illness, and with no late emergence of it during a median follow up period of 43 months,⁵ would have been named and defined with MPA, according to the CHCC. In fact, they should be considered as having a separate clinicopathological entity.

Even if patients with vasculitic pulmonary and/or renal syndrome (without granuloma formation) are differentiated as having MPA or INCGN or NAC or polyangiitis overlap syndrome or Wegener's syndrome, vasculitis, or disease^{1 6-8} it should not have any therapeutic implications as all them are forms of small vessel vasculitis. However, I believe that encompassing all cases under the name MAP or “polyarteritis” may be a confounding factor as it is regarded generally as the microscopic variant of (classic) PAN. In my opinion, the better term would be that denoting the essential clinicopathological or histopathological findings themselves. For instance, my group has proposed the name “necrotising glomerular and/or alveolar capillaritis”,² as in most cases only genuine capillaritis, as mentioned above, is demonstrated histologically. On the other hand, in the absence of granulomatous inflammation, and by extrapolation from ANCA distribution data in well defined conditions,^{1 2 9-11} one might argue that MPO-ANCA identify a limited or frustrated form of MPA in these idiopathic cases; on the contrary, detection of PR3-ANCA may indicate a localised form of WG.

A noteworthy finding in my study was the long interval between the initial presentation and the subsequent development of WG characteristic lesions. My main limitation is, obviously, the small number of patients (six) included. Thus, new terms are probably not justified on the basis of this small series. Nevertheless, I am not intending to suggest a different nomenclature but to raise some difficult questions regarding the above mentioned subset of limited vasculitis cases. My report may thus help illustrate the difficulty of applying diagnostic criteria/definitions for conditions of unknown aetiology and variable clinical presentation and course. Perhaps, a further revision of the systemic vasculitides nomenclature will help clarify some uncertainties coming not only from the CHCC nomenclature but also from the ACR classification. In fact, the 1990 ACR classification criteria have recently been found to function poorly in the diagnosis of specific vasculitides.¹² It should also be mentioned, however, that no time limits have been determined as to when a final diagnosis should be given. In any case, as some vasculitis cases do not necessarily stay the same along their course and can certainly evolve over time from one apparent diagnosis to another

later, follow up would be necessary to make a final diagnosis.

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