## Reclassification of polyarteritis nodosa based on the 1990 ACR criteria using the 2007 EMA algorithm modified by the 2012 CHCC definitions

Sirs,

Polyarteritis nodosa (PAN) is often confused with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), particularly microscopic polyangiitis (MPA). The 1990 American College of Rheumatology (ACR) criteria included no classification criteria for MPA and the 1990 ACR criteria for PAN did not mention ANCA positivity (1-3). To compensate for the 1990 ACR criteria, nomenclature of vasculitides was proposed by the Chapel Hill Consensus Conference (CHCC) in 1994 and 2012 (1, 4), and a new classification algorithm was suggested by the European Medicines Agency (EMA) in 2007 (5): PAN cannot be classified under ANCA positivity. In this study, we applied the 2007 EMA algorithm modified by the 2012 CHCC definitions (the modified EMA algorithm) to 32 Korean patients with PAN classified by the 1990 ACR criteria, and investigated whether they might be still reclassified as PAN or other types of vasculitides.

We retrospectively reviewed the electrical medical records of 32 patients with PAN according to the inclusion criteria as described in the previous study (6). This study was approved by the institutional Review Board (4-2016-0901). We divided 32 patients with PAN into 3 clinical variants (cutaneous, idiopathic generalised (classic) and hepatitis B virus (HBV)-associated PAN), and we applied the 2012 CHCC definitions to them to exclude patients. Subsequently, we applied the 2007 EMA algorithm modified by the 2012 CHCC definitions to excluded patients and reclassified them.

The results were summarised in Table I. All 6 patients with cutaneous PAN had histologic findings compatible with PAN without systemic involvement. We excluded 1 patient due to ANCA positivity (patient A) by the 2012 CHCC definitions. Despite no surrogate markers for granulomatosis with polyangiitis (GPA), patient A had histologic evidence of small-vessel vasculitis and could be reclassified as MPA by the modified EMA algorithm. This case provided a lesson that either histologic evidence of small-vessel vasculitis or ANCA positivity can suggest AAV even in patients with PAN classified the 1990 ACR criteria.

Among 10 patients with classic PAN, we excluded 5 patients due to ANCA positivity (patients B-F) by the 2012 CHCC definitions. All excluded patients had no surrogate markers for GPA or renal vasculitis. Although patient B and D had histologic findings compatible with PAN, and patients C, D and F showed typical arteriographic features of PAN, ANCA positivity reclassified them as unclassifiable vasculitis. ANCA positivity is a crucial step to reclassify patients with classic PAN by the modified EMA algorithm.

Among 16 patients with HBV-associated PAN, we excluded 3 patients by the 2012 CHCC definitions: 1 patient had MPO-ANCA and 2 patients had no arteriographic or histologic results (patients G-I). All excluded patients had no surrogate markers for GPA or renal vasculitis. Patient G with ANCA and patients H and I without arteriography or biopsy results were reclassified as unclassifiable vasculitis. Both ANCA positivity and the performance of arteriography or biopsy were critical steps to redistribute patients with HBV-associated PAN by the modified EMA algorithm. In addition HBV-associated PAN is currently classified as HBV-associated vasculitis by the 2012 CHCC definitions.

Thus, although 3 patients with HBV-associated PAN were reclassified as unclassifiable vasculitis, antiviral agents must be recommended to these patients (7).

Our study has several issues of the retrospective design and the low incidence of PAN. If future studies can serially enrol enough patients and prospectively apply the modified EMA algorithm to patients suspected of PAN, they may discover the most suitable modified criteria for Korean patients with PAN. In conclusion, we excluded 9 patients (28.1%) by the 2012 CHCC definitions and reclassified one patient as MPA and 8 patients as unclassifiable vasculitis the 2007 EMA algorithm modified by the 2012 CHCC definitions.

### Key messages

- We excluded 9 patients with PAN by the 2012 CHCC definitions.
- We reclassified one patient as MPA and 8 patients as unclassifiable vasculitis based on the 2007 EMA algorithm modified by the 2012 CHCC definitions.
- Both ANCA positivity and the performance of arteriography or biopsy were critical steps to classify patients suspected of PAN.

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**Table I.** Application of the 2007 EMA algorithm modified by the 2012 CHCC definitions to 9 patients, who fulfilled the 1990 ACR criteria for PAN, but not the 2012 CHCC definitions.

| Patients | Subclasses | The 1990 ACR criteria fulfilled* | Reason for exclusion based on the 2012 CHCC definitions | Items of the 2007 EMA algorithm modified by the 2012 CHCC definitions | |
|---|---|---|---|---|---|
| | | | | Clinical and histologic evidence of small-vessel vasculitis No GPA surrogate markers | None |
| | | | | Reclassified as MPA | Unclassifiable |
| A | cutaneous | 1, 4, 10 | MPO-ANCA &PR3-ANCA | Yes | |
| B | classic | 3, 4, 10 | MPO-ANCA &PR3-ANCA | | Yes |
| C | classic | 1, 6, 9 | MPO-ANCA &PR3-ANCA | | Yes |
| D | classic | 4, 5, 6, 7, 9, 10 | MPO-ANCA | | Yes |
| E | classic | 1, 4, 7 | MPO-ANCA | | |
| | | | No arteriography or biopsy | | Yes |
| F | classic | 1, 4, 5, 6, 7, 9 | MPO-ANCA | | Yes |
| G | HBV | 5, 6, 8, 10 | MPO-ANCA | | Yes |
| H | HBV | 5, 6, 8 | No arteriography or biopsy | | Yes |
| I | HBV | 1, 4, 8 | No arteriography or biopsy | | Yes |

*1: Weight loss ≥ 4 kg; 2: Livedo reticularis; 3: Testicular pan or tenderness; 4: Myalgia, weakness or leg tenderness; 5: Mononeuropathy or polyneuropathy; 6: Diastolic BP > 90 mmHg; 7: Elevated blood urea nitrogen or creatinine; 8: Hepatitis B virus; 9: Arteriographic abnormality; 10: Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils.

EMA: European Medicine Agency; CHCC: Chapel Hill Consensus Conference; ACR: the American College of Rheumatology; PAN: polyarteritis nodosa; MPO: myeloperoxidase; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody; HBV: hepatitis B virus.

# Letters to the Editors

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