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Interstitial pneumonia associated with MPO-ANCA: Clinicopathological features of nine patients

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Summary
Myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) is a well known marker for small vessel vasculitis. Recent reports have demonstrated that interstitial pneumonia (IP) may rarely be associated with serum MPO-ANCA. Yet, little is known about the histological features.

We reviewed surgical lung biopsy from nine patients with IP of uncertain etiology with serum MPO-ANCA.

There was a male predominance (6:3) with a median age of 62.1. Histologically, eight patients presented with a usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis, frequently accompanied by areas of nonspecific interstitial pneumonia (NSIP) pattern. One patient showed diffuse alveolar damage (DAD), and two patients showed mixture of UIP and DAD reflecting acute exacerbation of UIP. Microscopic honeycomb cysts were common, but fibroblastic foci were inconspicuous. The most frequent additional findings were small airway disease (9/9), and lymphoid follicles (7/9). Neither capillaritis nor vasculitis was seen in any of our cases. Three patients had microscopic hematuria, but none progressed to microscopic polyangiitis during the follow up. Mortality rate was 44% (median follow up 39.1 months).

IP associated with MPO-ANCA showed characteristic histology dominated by UIP pattern. Vasculitis was not identified in our cohort, but small airways disease and lymphoid follicles

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were present in most cases. IP associated with MPO-ANCA may be a histologically distinctive disease from idiopathic pulmonary fibrosis. Mortality was relatively high and life threatening acute exacerbation may occur.

Introduction

Serum myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) is not specific for any single disease and can be found in a variety of vasculitides, most commonly microscopic polyangiitis (MPA). However the precise biological mechanisms remain unknown.[1]

Recent reports have shown that some patients with interstitial pneumonia (IP) may have positive serum MPO-ANCA without developing known vasculitis. The number of publications on this topic is limited and the histological features of IP associated with serum MPO-ANCA have not been well-defined.[2] Based on existing reports, the majority of affected patients do not progress to MPA over the course of their disease.[3]

Newly published guidelines on the diagnosis and management of idiopathic pulmonary fibrosis (IPF) emphasize the importance of separating IPF from IP associated with specific systemic conditions such as those related to the collagen vascular diseases. If IP associated with MPO-ANCA is a distinctive form of pulmonary fibrosis, it should be separated from IPF. In that case, alternative therapy may be considered, especially since these individuals are not likely to qualify for clinical trials targeting IPF.[4]

In the present study, we describe the histopathologic findings and survival in a group of patients with IP associated with elevated serum MPO-ANCA.

Materials and methods

The pulmonary pathology consultation files of the Department of Surgical pathology, Toyama University Hospital, from 2008 to 2011, were reviewed in order to identify cases that showed interstitial pneumonia accompanied by elevated levels of serum MPO-ANCA. Clinical data, including age, gender, smoking history, symptoms, existence of MPA and follow up data were obtained from patient medical records. Laboratory and pulmonary function data at the initial presentation were also recorded. All patients were evaluated for the presence of autoimmune antibodies including anti-nuclear antibody (ANA), MPO-ANCA, and proteinase-3 (PR3)-ANCA. According to the Japanese guideline for idiopathic interstitial pneumonias,[5] basically all interstitial pneumonia cases are recommended to examine serum ANA, MPO-ANCA, PR3-ANCA and other autoimmune antibody as a routine screening test to exclude the collagen vascular disease from idiopathic interstitial pneumonias. In the guideline, the serum MPO-ANCA level of $>$20 EU is suggested to be positive.

Radiological review: high-resolution computed tomography (HRCT) scans of the chest at the time of biopsy were available for all patients. The HRCT scans were reviewed in a blinded fashion by a chest radiologist (R.E.) experienced in the interpretation of diffuse lung disease and were classified using the radiologic patterns described in the ATS/ERS International Consensus Classification 2002 of the Idiopathic Interstitial Pneumonias (IIPs).[6]

Histologic review: all lung biopsy specimens were reviewed independently by two pathologists (J.F., T.T.). Each biopsy was classified using the histopathologic patterns described in the ATS/ERS International Consensus Classification 2002 of the IIPs. In cases where there was disagreement, a consensus was established through further review. The following histologic features were semi-quantitatively graded: marked dense fibrosis (MF: $-$, absent; $+$ weak; $++$, strong), patchy fibrosis (PF: $-$, absent; $+$ weak; $++$, strong), honeycomb change (HC: $-$, absent; $+$, weak; $++$, strong), fibroblastic foci (FF: $-$, absent; $+$, weak; $++$, strong), capillaritis (CA: $-$, absent; $+$ weak; $++$, strong), vasculitis (VA: $-$, absent; $+$ weak; $++$, strong), lymphoid follicle with germinal center (LY: $-$, absent; $+$, weak; $++$,strong), small airway disease (SAD: $-$, absent; $+$, weak; $++$, strong). When small airway diseases were observed, they were divided into three subtypes, cellular, cellular and fibrotic, and fibrotic, depending on the predominance of inflammation and fibrosis. Follicular bronchiolitis was included in cellular bronchiolitis.

If other relevant histological findings (e.g. granuloma) were present, they were also documented. The evaluation for capillaritis and vasculitis was performed using slides stained with H&E and elastica van Gieson (EVG) stainings.

To understand the clinical outcome, a Kaplan Meier curve was plotted, and a median survival time was pointed out.

The study protocol was approved by the Institutional Review Board of Toyama University Hospital.

Results

Clinical findings

Among total of 272 cases sent from the three institutes for consultation to the pathology archive of interstitial pneumonia at Toyama University Hospital, 224 patients were available for MPO-ANCA levels at the time of biopsy. Out of those 224 patients, we identified nine patients showing higher levels of MPO-ANCA. PR3-ANCA levels were also tested for majority of patients at the time of biopsy, which showed 4 out of 219 patients were positive. Only one patient, patient 2, showed positive for both MPO and PR3-ANCA. Data of other autoimmune antibodies were also available at the time of biopsy, which showed positive for RF, 50/222; ANA, 41/227; SS-A, 20/216; Jo-1, 10/231; RNP, 6/151; Scl-70, 2/215 and SS-B, 1/194.The mean age of elevated serum MPO-ANCA patients was 62.1 years with a male predominance (M:F = 6:3). Three patients demonstrated microscopic hematuria, while two patients who were detected on a health check-up had no symptoms. A