Case report

Myeloperoxidase anti-neutrophil cytoplasmic antibody-associated vasculitis with a unique imaging presentation of organizing pneumonia: A case report

Kazufumi Takada, MD a,1, Atsushi Miyamoto, MD, PhD a,6,7, Hiroshi Nakahama, MD a, Shuhei Moriguchi, MD a, Yui Takahashi, MD a, Kazumasa Ogawa, MD a,2, Kyoko Murase, MD a, Shigeo Hanada, MD, PhD a,3, Nasa Morokawa, MD, PhD a, Atsuko Kurosaki, MD b, Takeshi Fujii, MD, PhD a,4, Eiko Hasegawa, MD b,6, Hisashi Takaya, MD, PhD a,3, Daiya Takai, MD, PhD a,6,8

ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) constitutes a group of blood vessel inflammation diseases of autoimmune origin. Myeloperoxidase (MPO) ANCA is closely related to ANCA associated AAV. The MPO-ANCA positive AAV patients have lung involvement at high rates; however, there are only a few reported cases with organizing pneumonia (OP). A 78-year-old man was presented to our hospital due to a fever of 38 °C despite a whole month of antibiotics treatment. Chest computed tomography image revealed restricted consolidations visible in the middle lobe of the right lung and the upper lobe of the left lung, which suggested an OP pattern. MPO-ANCA and urine occult blood tests were positive. Histopathological examination of the transbronchial biopsy revealed OP and mucus plug. Histological findings on renal biopsy showed necrotizing glomerulonephritis related to AAV. The patient was diagnosed with MPO-ANCA positive AAV and was treated with systemic corticosteroid therapy, from which he recovered rapidly. Thus, when diagnosing OP, the possibility of AAV should be considered by ordering patients’ serum ANCA and occult hematuria tests.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis (AAV) is a group of vasculitis that mainly affects small blood vessels. AAV mainly consists of three disease states microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. MPO-ANCA is strongly related to these diseases, and show high positivity, especially in MPA. AAV is a disease that involves multiple organs, including the kidney and the lung, which are most frequently damaged under this condition [2]. Interstitial pneumonia (IP) is often revealed by computed tomography (CT) in MPO-ANCA-positive AAV patients. Honeycomb changes are most frequently presented in these patients and are typical features of usual interstitial pneumonia (UIP) pattern [3,4]. However, our patient presented with organizing pneumonia (OP) pattern, which is rare in MPO-ANCA positive AAV patients [5,6]; therefore, we considered it...
imperative to describe his case in this presentation.

2. Case report

A 78-year-old man was admitted to our hospital with a recent history of persistent fever with 38 °C, suspicious of infection. Prior to the admission, a general physician had started treatment with cefcapene pivoxil and ibuprofen five days after the patient’s fever start; however, there was no improvement. Two weeks (15 days) later, the physician changed the medications to ciprofloxacin and acetaminophen as a result of the poor efficacy of the initial prescription. Three days later, he visited our hospital, which was 23 days after the initial fever. He had neither smoking habit nor a history of exposure to asbestos. His past medical history was appendicitis, hypertension, and atrophic gastritis. The patient worked as a university professor prior to his retirement, and he had no history of occupational exposure that might be associated with MPO-ANCA.

The following were the data gathered in the course of his physical examination: Height: 178 cm, weight: 56 kg, body mass index (BMI): 17.7, body temperature: 38.0 °C, and SpO2: 97% at room air. Moreover, the patient presented with occasional mild dry cough and grade 3 dyspnea on exertion based on the Modified Medical Research Council dyspnea scale. Pitting edema was observed on both lower legs, the lung sound was clear, there was no presentation of oral ulcer, bloody nasal discharge, hearing loss, skin eruption, and no symptoms suggestive of upper airway manifestations. Based on the detailed characteristics, pitting edema on the lower extremities was considered as fast edema. The blood test showed elevated white blood cell counts of 9500/μL (90.5% neutrophils, 4% lymphocytes, 4% eosinophils). C-reactive protein (CRP) was 12.5 mg/dL, albumin level was 2.3 g/dL, and creatinine level was 0.87 mg/dL. A urine test showed protein (1+) and occult blood (3+) positive (Table 1). The CT findings revealed peripheral and peribronchovascular consolidation with patchy non-segmental distribution and air-bronchogram. These lesions showed relatively homogeneous CT density in the mediastinal window, even without enhancement by a contrast media. The features were considered to correspond to OP pattern (Fig. 1a and b); hence, the patient was hospitalized.

In-patient treatment was started with intravenous ampicillin/sulbactam administration (1.5 g every 6 hours); however, the pulmonary consolidations expanded, indicating bilateral pleural effusion. The fever continued and his general condition worsened. Serum MPO-ANCA level increased to 16.7 IU/ml, while anti-proteinase-3 ANCA and antinuclear antibodies were negative. Histopathological examination of the transbronchial biopsy revealed OP lesion with separately observed mucus plug (Fig. 2a,b,c); however, there was no evidence of granuloma formation, extensive eosinophilic infiltration, alveolar hemorrhage, and vasculitis. The histopathological examination of the renal biopsy showed segmental collapse, inflammatory cell infiltration, and crescent formation in one glomerulus, suggesting underlying AAV (Fig. 2d and e), and the patient was diagnosed with MPO-ANCA positive AAV.

Due to physical exhaustion associated with uncontrolled inflammation, edema rapidly declined. The patient’s weight rapidly increased from 56 kg on the 1st day to 59 kg on the 10th day of hospitalization (32 days after the initial presentation of fever). His serum albumin level decreased from 2.3 g/dL on the 1st day to 1.4 g/dL on the 10th day of hospitalization. Then, the patient developed respiratory failure due to pulmonary congestion. Hence, supplemental oxygen therapy at 1–2 L/min via nasal cannula was started. Further, the patient’s general status declined even when he stayed on bed during most of the day. Then, he presented with bilateral pleural effusion (Fig. 1c and d); thus, thoracentesis was performed. According to the Light criteria, the patient presented with transudate pleural effusion. The serum lactate dehydrogenase (LD) and total protein (TP) levels were 169 and 5.5 g/dL, and the pleural LD and TP levels were 73 and 2.1 g/dL, respectively. The treatment for AAV involved undertaking steroid pulse therapy with 1000 mg of methylprednisolone for three days on the 10th day of hospitalization due to the rapid decline in his general and respiratory status, followed by daily prednisolone therapy with 0.5 mg/kg/day. The therapy improved the patient’s general condition; serum CRP and MPO-ANCA level decreased rapidly and gradually. On the 3rd day after starting steroid pulse therapy, the patient’s body temperature normalized. Further, his respiratory status recovered; thus, supplementary oxygen therapy was discontinued. On CT imaging, consolidation improved significantly and bilateral pleural effusion disappeared on the 13th day after the initiation of steroid pulse therapy (45 days after the initial presentation of fever) (Fig. 1e and f). The patient’s body weight also decreased to 50 kg, and the serum albumin level was still elevated at 2.5 g/dL. Then, the patient fully recovered. We have since reduced the dosage of oral prednisolone gradually and observed no relapse for approximately one year.

3. Discussion

AAV is a disease that damages multiple organs such as the lungs and kidneys. In particular, the lung is of the organ that is typically damaged, and in some cases, it is the initial clinical manifestation for AAV diagnosis. Especially, in Japan, MPO-ANCA-positive AAV is known to have a high rate of IP [7]. UIP pattern is typical both on CT image and histopathological display of MPO-ANCA-positive AAV patients [4]. While UIP is a common pathological lesion suggesting a chronic disease process, diffuse alveolar hemorrhage is a typical pathologic lesion suggesting an acute disease process in AAV in patients with MPA [8]. In contrast, reports have indicated that pathologically proven OP lesion association with MPO-ANCA is scarce [5,6]. Additionally, our multidisciplinary discussion based on CT and biopsy findings suggested that the OP lesion was a suitable underlying pathological change rather than granuloma formation.

| Table 1 | Laboratory findings in hospitalization. |
|--------------------------------|-----------------------------------|
| **Chemistry** | **Blood** |
| TP 6.4(L) g/dL | WBC 9500(H) /μL |
| Alb 2.3(L) g/dL | RBC 3.21(L) x10⁹/μL |
| CK 220(L) U/L | Hb 10.0(L) g/dL |
| AST 21 U/L | Ht 30.4(L) % |
| ALT 17 U/L | MCV 94.7 fl |
| LD 135 U/L | MCH 31.2 pg |
| ALP 296 U/L | MCHC 32.9 g/dL |
| γGT 46 U/L | Pr 32.9 10⁵/L |
| INR 15 mg/dL | <Immune system> |
| Cr 0.87 mg/dL | MPO-ANCA 16.7(H) IU/mL |
| UA 4.6 mg/dL | PR3-ANCA <0.5 IU/mL |
| TG 51 mg/dL | IgG 1325 mg/dL |
| TC 95(L) mg/dL | IgM 120.2 mg/dL |
| LDL-C 58(L) mg/dL | IgA 498.2(H) mg/dL |
| HDL-C 23(L) mg/dL | C3 82 mg/dL |
| Na 134 mmol/L | C4 5(L) mg/dL |
| K 4.4 mmol/L | CH50 23(L) U/mL |
| Cl 96(L) mmol/L | R3-6 131 L/mL |
| Ca 2.82(L) mg/dL | SP-D 43.3 ng/mL |
| Fe (L) μg/L | <Hormonal system> |
| UBBC 139(L) μg/L | Ferritin 511(H) μg/L |
| CRP 12.49(H) mg/dl | TSH 2.591 μIU/mL |
| <Coagulation> | Free-T₄ 1.19 ng/dl |
| aPTT 33.6 Sec | BNP 187.7(H) pg/mL |
| PT INR 1.10 | <Urine test> |
| D-dimer 3.7(H) mg/ml | pH 5.5 |
| <ABG> | Glu (–) |
| pH 7.49 | Prot (1-1) |
| PaO₂ 36 mmHg | OB (3-) |
| PaCO₂ 81 mmHg | Bil (–) |
| HCO₃ 28 mmol/L | Uro (–) |
| SaO₂ 96.6 % | Segmentation |
| Condition Room air | RBC >50 /μL |
| WBC 1.4 /μL | Epi <1 /μL |
The mechanism by which MPO-ANCA occurs with IP and fibrosis is not clear. One hypothesis is that the direct effects of ANCA on neutrophil causes the vascular endothelial cell injury and minimal alveolar hemorrhage, which, in turn, are the possible causes of the fibrosis and chronic IP presenting UIP pattern in patients with MPA. However, no evidence of co-existence of hemorrhage superimposed to honeycomb fibrosis has been observed [9,10]. In our case, there was no pathological evidence of acute alveolar hemorrhage, such as hemosiderin-phagocytic macrophages. Therefore, it remains inconclusive whether the aforementioned hypothesis would apply to an OP lesion as a reactive pathologic process in the acute or subacute stage of AAV.

MPO-ANCA is related to airway lesions such as bronchial wall thickening or bronchitis [11], which admixture with consolidation and ground-glass opacity around the honeycomb lungs could be observed even in patients with UIP pattern. These findings might also represent inflammatory cellular infiltration to the lung parenchyma [12].
Pathologically, the presence of bronchiolitis is often recognized along with the formation of lymphoid follicles [4]. In our case, the mucus plug was observed in the transbronchial biopsy specimen, suggesting the presence of bronchiolitis. Although the bronchiolitis feature was not clear on the CT images, our patient had a characteristic MPO-ANCA-positive pathology.

A spontaneous improvement case of OP associated MPO-ANCA has been reported [5]. Nonetheless, with regards to our case, the deterioration of the general condition improved rapidly via steroid treatment, unlike the clinical course in the previous report that indicated the need for aggressive therapies.

In conclusion, the mechanism of OP at the MPO-ANCA-positive patients remains unclear, and there have been only a few reports that OP was clinically diagnosed in patients with MPO-ANCA associated AAV, even in case reports. Thus, the accumulation of cases is needed. In clinical practice, the possibility of AAV should be considered when treating patients with OP.

Funding

No funding was used to acquire the information/data described in this case report.

Ethics approval and consent to participate

This study was carried out following the Code of Ethics Declaration of Helsinki of the World Medical Association.

This case report was approved by the local Ethics Committee of Toranomon Hospital (approval number #2074, Aug./19th/2020).

Consent for publication

Written informed consent for publication of this case report and the associated images was obtained from the patient.

Declaration of competing interest

The authors declare no competing interests.

References

[1] J.C. Jennette, R.J. Falk, P.A. Bacon, N. Banu, M.C. Cid, F. Ferrario, L.F. Flores-Suarez, W.L. Gross, L. Guillevin, E.C. Hägen, G.S. Hoffman, D.R. Jayne, C. K. Takada et al.
[2] A. Millet, M. Federzoli-Ribeil, L. Guillevin, V. Winko-Sarsat, L. Mouthon, Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group? Ann. Rheum. Dis. 72 (2013) 1273–1279, https://doi.org/10.1136/annrheumdis-2013-203255.
[3] S. Homma, H. Matsuishi, K. Nakata, Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides, Respirology 9 (2004) 190–196, https://doi.org/10.1111/j.1440-1843.2004.00581.x.
[4] T. Tanaka, K. Otani, R. Egashira, Y. Kashima, H. Taniguchi, Y. Kondoh, K. Katoaka, A. Shiraki, Y. Kitasato, K.O. Leslie, J. Fukuoka, Interstitial pneumonia associated with MPO-ANCA: clinicopathological features of nine patients, Respir. Med. 106 (2012) 1765–1770, https://doi.org/10.1016/j.rmed.2012.08.024.
[5] S. Imokawa, M. Uehara, T. Uto, J. Sato, T. Suda, Organizing pneumonia associated with myeloperoxidase anti-neutrophil cytoplasmic antibiotic, Respirol Case Rep 3 (2015) 122–124, https://doi.org/10.1002/rcr2.123.
[6] P.B. Gaudin, F.B. Askin, R.J. Falk, J.C. Jennette, The pathologic spectrum of pulmonary lesions in patients with anti-neutrophil cytoplasmic autoantibodies specific for anti-proteinase 3 and anti-myeloperoxidase, Am. J. Clin. Pathol. 104 (1995) 7–16, https://doi.org/10.1093/ajcp/104.1.7.
[7] S. Ozaki, T. Atsumi, T. Hayashi, A. Ishizu, S. Kobayashi, S. Kumaga, Y. Kurihara, M.S. Kurokawa, H. Makino, H. Nagafuchi, K. Nakabayashi, N. Nishimoto, M. Suka, Y. Tomino, H. Yamada, K. Yamagata, M. Yoshida, W. Yamura, K. Amano, Y. Arimura, K. Hatta, S. Ito, H. Kikuchi, E. Muso, H. Nakashima, Y. Ohosone, Y. Suzuki, H. Hashimoto, A. Koyama, S. Matsuo, H. Kato, Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study, Mod. Rheumatol. 22 (2012) 394–404, https://doi.org/10.1080/10496138.2011.563421.
[8] S. Homma, A. Suzuki, K. Sato, Pulmonary involvement in ANCA-associated vasculitis from the view of the pulmonologist, Clin. Exp. Nephrol. 17 (2013) 667–671, https://doi.org/10.1007/s10157-012-0710-7.
[9] L.F. Flores-Suarez, Limited pulmonary MPA, a new MPA entity? A rheumatologist’s perspective, Clin. Exp. Nephrol. 17 (2013) 672–675, https://doi.org/10.1007/s10157-012-0732-5.
[10] J. Birzbaum, S. Danoff, F.B. Askin, J.H. Stone, Microscopic polyangiitis presenting as a “pulmonary-muscle” syndrome: is subclinical alveolar hemorrhage the mechanism of pulmonary fibrosis? Arthritis Rheum. 56 (2007) 2065–2071, https://doi.org/10.1002/art.22632.
[11] M. Yamagata, K. Ikeda, K. Tsushima, K. Iesato, M. Abe, T. Ito, D. Kashiwakuma, Y. Arimura, H. Yamada, K. Yamagata, H. Sugiyama, S. Kagami, I. Iwamoto, D. Nakagomi, T. Sugiyama, Y. Maruyama, S. Furuta, D. Jayne, T. Uno, K. Tatsuki, H. Nakajima, Prevalence and responsiveness to treatment of lung abnormalities on chest computed tomography in patients with microscopic polyangiitis: a multicenter, longitudinal, retrospective study of one hundred fifty consecutive hospital-based Japanese patients, Arthritis Rheum. 68 (2016) 713–723, https://doi.org/10.1002/art.39475.
[12] A. Suzuki, S. Sakamoto, A. Kurosaki, Y. Kurihara, K. Satoh, Y. Usui, T. Nanki, Y. Arimura, H. Makino, Y. Okada, M. Harigai, K. Yamagata, H. Sugiyama, H. Dobashi, A. Ishizu, N. Tsuibo, J. Usui, K.E. Sada, S. Homma, Chest high-resolution CT findings of microscopic polyangiitis: a Japanese first nationwide prospective cohort study, AJR Am. J. Roentgenol. (2019) 1–11, https://doi.org/10.2214/ajr.18.20967.