Rituximab ameliorated PR3-ANCA positive vasculitis with rheumatoid arthritis simultaneously

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May 6, 2020

Abstract

We treated PR3-ANCA positive vasculitis patient with bilateral ischemic peroneal nerve paralysis accompanying rheumatoid arthritis. Pathology showed mild vasculitis. With PR3-ANCA amelioration, the level of complement 3, anti-CCP and neurological disability normalized simultaneously responding to rituximab. This result means the shared pathogenic pathway of PR3-ANCA vasculitis and rheumatoid arthritis.

Rituximab ameliorated PR3-ANCA positive vasculitis with rheumatoid arthritis simultaneously

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Abstract

We treated PR3-ANCA positive vasculitis patient with bilateral ischemic peroneal nerve paralysis accompanying rheumatoid arthritis. Pathology showed rare to mild vasculitis. Along with PR3-ANCA amelioration, the level of complement 3, anti-CCP and neurological disability normalized simultaneously responding to rituximab (anti-CD20 monoclonal antibody RTX) therapy. This could be clue to clarify the shared pathogenic pathway of PR3-ANCA vasculitis and rheumatoid arthritis

Key Words

PR3-ANCA positive vasculitis, rheumatoid arthritis, Rituximab

Key clinical message

We treated PR3-ANCA positive vasculitis patient with rheumatoid arthritis. By applying monoclonal antibody therapy patients suffering more than one collagen disease are relieved at the same time from collagen diseases. That is pathogenic pathways are shared among collagen diseases.

Introduction

PR3-ANCA positive vasculitis is generally known as granulomatosis with polyangiitis (GPA) with autoimmune small vessel necrotization. The clinical manifestations of GPA usually include in paranasal sinuses, lung

and kidney. We treated a PR3-ANCA positive vasculitis presenting rare manifestation of ischemic peroneal nerve paralysis complicated with rheumatoid arthritis by monoclonal antibody (rituximab) therapy.

To our knowledge, successful RTX therapy against PR3-positive vasculitis with rheumatoid arthritis at the same time has never been reported in literature to date.

Case presentation

An eighty-year-old female admitted to our hospital on 25st Jul in 2014 with intermittent fever above 39.0 centigrade degree for the last a few months. In previous hospital, she was diagnosed development of rheumatoid arthritis (Stage V Class III, four swollen joints and seven tender joints) and intake of methotrexate was up to 6mg from 4mg/week. Nevertheless, morning stiffness, joint pain of bilateral shoulder, elbow, wrist and fever continued. On admission to our hospital computed tomography showed infiltrative shadow in right lower bronchi and bronchiectasia presenting the history of paragonimiasis. First we suspected bronchilitis of bacterial infection and administered antibiotics (Tazobactam/Piperacillin) for two weeks in vain. Several days after admission to our hospital, she bled slightly from right nasal cavity once. As the level of titer of antibody to myeloperoxidase 3 showed so high soon, we suspected GPA secondly (Table). On 1st Sep we biopsied right peroneal paralytic vasculitic lesion with disability of dorsal flexion caused by vasculitic ischemia. She presented slight nasal bleeding, intermittent fever, body weight loss polyneuritis of lower extremities. Pathological examination showed pauci-immune vasculitis and granuloma is formed outer side of adventitia of vasculitis leading to the diagnosis of PR3-ANCA positive vasculitis (Fig.4) clinically (1).

On 17th Sep, 24th Sep and 1st Oct, this patient received 495mg of rituximab standard loading therapy. Three days after third administration, she experienced melena diagnosed as cytomegalovirus colitis. Valgancyclovir was prescribed and recovered soon. On 19th Feb, for maintenance therapy, 495mg of RTX was executed with valgancyclovir (Fig1). With this loading therapy, she was afebrile caused by ANCA-associate vasculitis and she got better from swollen and tender joint of rheumatoid arthritis. Four months after admission her rheumatoid arthritis flared, we add methotrexate. From admission to our hospital she was taking physical therapy with ankle supportive devices. Three years after RTX therapy her peroneal nerve paralysis steadily recoverd to fair (3/5) from trace (1/5) of manual muscle test.

Discussion

The aetiological background HLA genes of GPA is reported HLADPB1 *04:01(2, 3). Of this patient, HLADPB1 is *04:02:01 and *05:01. It is unique to this patient. Computed tomography didn't show vasculitic lesions in nasal and maxillary sinuses in spite of nasal bleeding nor lung field. This didn't show respiratory involvements. Urinalysis showed no proteinuria nor hematuria (Table). She was suffering intermittent fever for at least a few months and lost bodyweight from about 50kg to 40kg for the six months before hospitalization. She was aware of paralytic disability of dorsal flexion of both ankles. Pathological examination from suffered peroneal artery revealed thrombotic or apparent granulomatous tissue in adventitia suggesting umbiguous GPA. In case of GPA, granulomatous tissue is in the elastic lamina media. The titer of PR-3 ANCA is high (170 U/ml). We conclude that she is suffering PR3-ANCA positive vasculitis associated with rheumatoid arthritis on both lower legs.

Immune histopathological examination showed pauci-immune vasculitis. That is, CD3 positive T cells and CD68 positive or CD163 positive macrophages apparently invade. CD138 positive plasma cells existed outer area of adventitia. C3 staining was slightly positive.

It is difficult to differentiate histology between GPA and rheumatoid vasculitis. Rheumatoid vasculitis has serological feature of lower level of circulating immune complex, von Willebrand factor antigen, ICAM-1, VCAM, E-selectin c fibronectin, IgM RF, IgG RF and IgA RF compared with rheumatoid arthritis(4). In this case we couldn't detect immune complexes, IgG RF on admission (Table).

Rheumatoid vasculitis is important different diagnosis of ANCA-associated vasculitis. Hypocomplementemia is shared among GPA, rheumatoid vasculitis and systemic lupus erythematosus. But the titer of anti-PR3

ANCA is high, pauci-immune vasculitis is eminent and no circulating immune complex, no symptom suggesting SLE. From these results, we diagnosed granulomatosis with polyangiitis complicated with rheumatoid arthritis.

She was afebrile just after taking first RTX infusion on 17th September. The titer of anti-PR3-ANCA decreased from 142U/ml to 78.4U/ml in four months. We were to add administering standard dose of RTX every 6 months as maintenance therapy (5). The level of titer of anti-PR3-ANCA gradually went down again with maintenance RTX therapy to 85U/ml (1st Apr). Hypocomplementemia was gradually ameliorating. Among complements, C3 went up to normal range on 18th Nov. C4 was recovering slowly (2nd Feb) (Fig2). GPA activates alternative pathway of complement(6). ANCA associated renal lesion also related to complement pathway(7). GPA could be reflecting the level of C3.

Clinical symptom of rheumatoid arthritis was getting better with loading RTX(Fig 3). The neurological recovery of standard maintenance therapy of RTX against GPA is not well known. Neurological deficit of polymononeuritis seems to following amelioration of vasculitis. AAV often occurs with significant delay from the first rheumatological manifestations(8). Preceding mechanism of complication of AAV with RA is genetic disposition. The points are HLA region, PTPN22 ((9) (10) (11) (12)), polymorphism of uteroglobin (13) and of NF-$\varkappa$B2.

The risk of lymphoproliferative disorder is higher than general population with or without reactivation of EB virus with methotrexate (14). We couldn't detect EB virus activation nor abnormal accumulation of radioisotope from PET CT on admission.

For the six months of RTX therapy, granulomatosis of polyangiitis was improving slowly. The level of complement is normalizing monthly. In patients with MPO-ANCA related nephropathy low level of C3 means poor prognosis (15) . This case vasculitis is mild and localized lower legs atypically. If we could follow the natural course of this patient, symptoms of nose, lung, kidney lesions could occur afterward. Federico reported the BVAS is an excellent tool for assessing the in-ICU mortality risk of patients with systemic vasculitis (16). In case of senile patient adverse event of RTX is more important to mortality than BVAS assessment. We need more sensitive marker of granulomatosis of polyangiitis than MPO-ANCA. With the improvement of PR3-ANCA positive vasculitis with RTX therapy, serological data reflecting RA activity were getting better especially in loading phase (17).

Conclusion

We treated PR3-ANCA positive vasculitis patient with rheumatoid arthritis. This patient got better from both collagen diseases simultaneously. This could be clue to clarify the shared pathogenic pathway of PR3-ANCA vasculitis and rheumatoid arthritis.

Acknowledgments

Thanks to Eijiro Adachi for biopsying vasculitic lesion of peritoneal neuritis in left lower limb.

Thanks to Tatsuhiko Miyazaki for immunostaininig of biopsied specimens.

Published with written consent of the patient.

Conflict of interest

None.

Author Contributions

YA, SA and OY performed the patient care and collected clinical information and blood samples. YA and OY coordinated this study and wrote the paper.

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