Multiple Intracranial Nodules Associated with Rheumatoid Arthritis: Case Report

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Abstract

A 71-year-old woman with active rheumatoid arthritis (RA) was referred to our department because of multiple intracranial nodules. On admission, the RA disease activity was very high even after the treatment of methotrexate in other hospital. She underwent open biopsy to confirm a histopathological diagnosis of the intracranial lesions. Surgical specimen mainly consisted of necrosis surrounded by epithelioid cells. The masses were reduced spontaneously in size without additional treatment. Eleven month later, the lesions were relapsed. She underwent treatment with corticosteroid, and the lesions were remarkably regressed. The clinical course and histological examination were compatible with rheumatoid nodule (RN). Intracranial RN is extremely rare and its clinical course is not completely understood. In active RA patients, RNs should be considered, and histological diagnosis is inevitable for following suitable treatment.

Key words: intracranial granulation, choroid plexus, corticosteroid, long term follow-up, rheumatoid nodule

Introduction

Rheumatoid arthritis (RA) is a systemic disease that affects nearly every organ. Nodule formation is observed in 20% of the patients with RA.1,2 It usually develops subcutaneously, but is rarely seen in various organs such as pleura, lung, and pharynx. On the other hand, central nervous system involvements such as vasculitis, hypertrophic pachymeningitis, or leptomenigitis rarely occur. It is often difficult to diagnose.2 Therefore, intracranial rheumatoid nodule (RN) has been rarely identified, and its clinical course and optimal treatment are not determined. We, here, present a case of intracranial multiple RNs that have been successfully treated with corticosteroid. We describe the clinical course, discuss the pathogenesis, and treatment of the intracranial RN.

Case Report

A 71-year-old woman had suffered from RA since August 2005. She started to take 4 mg of methotrexate (MTX) per week in November 2005. Because the arthritis was uncontrolled, MTX was increased up to 8 mg/week and the symptoms were gradually improved. However, the dose of MTX had to be decreased because of liver dysfunction. Alternatively, she was treated with decreased dose of MTX and other conventional therapy for RA such as salazosulfapyridine or bucillamine, which were neither effective. Therefore, she was referred to our University Hospital for further treatment in December 2006. On admission, rheumatoid factor was negative, but the 28-joint disease activity score (DAS-28) was 6.55. She underwent whole body examination by computed tomography (CT) for screening before the introduction of a newly developed therapeutic agent. Computed tomograms disclosed a mass with calcification in the posterior fossa, but not extra-cranial lesions. Magnetic resonance (MR) imaging showed multiple intracranial masses and they were strongly enhanced with contrast medium (Fig. 1a–d). The intracranial masses were located in the right cerebello-pontine angle, in the floor and posterior part of third ventricle, around bilateral foramens of Lushka, around bilateral Meckel’s caves, and superior to left hippocampus. Some of them were attached to the dura mater and others were located adjacent to the choroid plexus. Abnormal high intensity area on T1-weighted image was seen in the brain parenchyma around the masses. The lesions strongly suggested dissemination of primary or metastatic brain tumor. Induction of new drug for RA was
abandoned, and she was transferred to the neurosurgical department to confirm the histological diagnosis.

Her general status was good and no neurological deficits were observed. The specimen was taken from the biggest mass located in the right cerebello-pontine angle. The lesion was grayish-white, avascular, and amorphous. The surgical specimens histologically consisted of coagulative necrosis surrounded by epithelioid cell granulomas with a few multinucleated giant cells including Langhans-type (Fig. 2a, b). Gram-stain did not show any microorganisms and it was diagnosed as a sort of granulation. It was strongly speculated that the lesions were associated with RA, but treatments targeting on the lesions were not performed because the exact etiology was not determined. She continued the treatment for RA with 8 mg/week of MTX. MR imaging taken 1 month after surgery disclosed that all the masses got reduced in size and she was followed up at the outpatient clinic. The masses continued to shrink for the next 6 months (Fig. 3a, b) as observed under MR imaging.

Three months later, she became lethargic, and neurological examination showed right hearing disturbance and mild limb ataxia. MR imaging showed regrowth of the masses (Fig. 4a–d). RA at that moment was not active. Therefore, RA itself did not require further treatment. She was treated with predonisolone since the lesions were inflammatory granulomas. She gradually got better and became active. Limb ataxia disappeared, though gait disturbance was not completely improved. MR imaging taken 2 weeks after the induction of predonisolone showed remarkable shrinkage of all masses. The lesions kept shrinking and the granulomas almost disappeared except calcification in 3 years (Fig. 5a–c). Consequently, we diagnosed the lesions as the RN. Predonisolone was tapered off over a period of 30 months and her general condition was stable after discontinuation of predonisolone.

Discussion

RNs are the most common extra-articular lesions that occur in 20% of RA patients. Most commonly RNs occur subcutaneously, and also develop in various organs in the body such as lungs, pleura, and larynx.

Intracranial RNs are very rare and the clinical course is not well understood. According to our survey of...

![Fig. 1 a: Initial T1-weighted magnetic resonance imaging with gadolinium. Well-enhanced nodules at bilateral foramen Lushka. b: The largest calcified mass in cerebello-pontine cistern showing mass effect. c: Coronal view showing enhanced lesions in the floor of third ventricle and adjacent to the left hippocampus. d: Sagittal section showing abnormal enhancement in the floor and posterior wall of third ventricle.](image1.png)

![Fig. 2 Photomicrograph showing necrosis surrounded by epithelioid cells (a) with few multinucleated giant cells (b). Hematoxylin and eosin stain.](image2.png)
Multiple Intracranial Rheumatoid Nodules

MR imaging followed up for more than 3 years.

Histopathologically, RN is characterized by fibrinoid necrosis surrounded by nuclear palisading. Infiltration of inflammatory cells including plasma cells, lymphocytes, and eosinophils are in its peripheral. It is generally believed that RN is one of the consequences of rheumatoid vasculitis. According to the previous report, histopathological examination disclosed that various intracranial lesions such as rheumatoid encephalopathy, meningitis, or nodule could appear at the same time. Therefore, all those lesions may occur through the same mechanism.

Immunohistochemical examination showed deposition of IgG or IgM in the affected cerebral vessel wall and choroid plexus. Immune complexes may be trapped by choroid plexus as a result of filtration mechanism. MR imaging of our case showed abnormal signal intensity in the brain parenchyma around the nodules, which may suggest the vasculitis or encephalopathy.

Steroid therapy for intracranial lesions in RA seems to be effective. In our case, the lesions were reduced without additional treatment at the initial manifestation. Such evidence has not been reported previously. At the recurrence, we decided to treat the patient with prednisolone because of manifestation of neurological deficits, and the steroid therapy was thought to be effective for inflammatory

Fig. 3  T1-weighted magnetic resonance imaging with gadolinium enhancement taken one month after the biopsy. All the masses remarkably reducing in size (a, b).

Fig. 4  Magnetic resonance (MR) imaging taken 9 months after the biopsy showing the recurrence of the masses. T1-weighted MR imaging showing remarkable high intensity in bilateral peduncle and thalamus (a, b). T1-weighted MR imaging showing regrowth of the pre-existed masses (c, d).

Fig. 5  Final magnetic resonance (MR) imaging after steroid therapy. a: T1-weighted MR imaging with gadolinium enhancement showing minimal enhancement of the choroid plexus and b, c: disappearance of abnormal enhancement of the cerebellar pontine angle and third ventricle.
granuloma. Subsequently, we concluded that the lesions were associated with RA since the clinical course and histological findings were compatible for RN. In this case, RN formation was not associated with activity of RA, but it was probably important for the onset of the nodules.

Most of intracranial RN cases were reported before 1990. MTX was approved for RA treatment in the late 1980s and control of RA became dramatically improved with MTX. It is speculated that incidence of intracranial RN was diminished due to the MTX treatment. Further reduction of the incidence will be expected with the newly developed treatment for RA such as rituximab.

RN can occur during methotrexate therapy and it is called as MTX-induced accelerated nodulosis. It can be distinguished from spontaneous RN by the clinical course and immunohistochemical findings. Patients of RA develop RN rapidly after the induction or increasing of MTX and reduction of the dose induces rapid regression of RN. In some reports, it is positive for human leukocyte antigen (HLA)-DR4 though spontaneous RN did not. Difference may also be detected by expression of MMP-3, MMP-9, and Ki-67. Our case probably developed as spontaneous RNs because they resolved with continuation of MTX. In conclusion, RA can cause intracranial multiple nodules especially adjacent to dura mater and/or choroid plexus.

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