Clinical Case Report

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Methotrexate-associated primary hepatic lymphoma and cranial neuropathy in a patient with rheumatoid arthritis

A case report with clinical follow-up over a 7-year period

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Abstract

Rationale: Rheumatoid arthritis (RA) shows a variable clinical expression in patients. Articular disease is common manifestation, but patients may rarely present with extra-articular manifestation such as cranial neuropathy. Also, primary hepatic lymphoma (PHL) has rarely been reported in patient treated with immunosuppressive drug such as methotrexate (MTX) for RA. We herein describe a case of cranial neuropathy and MTX-related PHL in a woman receiving MTX for RA.

Patient concerns: A 73-year-old women received MTX treatment for more than 5 years, presented with recurrent cranial neuropathies. During therapy of cranial neuropathies, liver enzyme levels were elevated.

Diagnoses: The patient was diagnosed as RA by laboratory examination. A series of examinations had been launched to evaluate any possible cause of the extra-articular manifestation of the patient including ultrasound, computed tomography, magnetic resonance image (MRI) and positron emission tomography of the liver and MRI of the brain. Finally, the patient diagnosed as MTX-associated PHL and cranial neuropathy.

Interventions: The patient underwent 4-year MTX therapy for RA at first with prednisolone. After that, she had been treated with cyclophosphamide therapy for cranial neuropathy. The liver biopsy was performed for hepatic lesion.

Outcomes: MTX was discontinued, but no improvement of PHL and elevated liver enzyme was observed during the 3 weeks. The patient received 6 cycles of chemotherapy for 3 months and achieved complete remission including PHL and cranial neuronal lesion with symptom. No instances of relapse have occurred in 2 years of follow-up.

Lessons: The present case is the extremely rare case in which MTX-related PHL and cranial neuropathy were involved together in the RA patient. It is necessary to examine long-term follow up hepatic and neurologic examinations that patient had a long history of receiving MTX therapy for RA.

Abbreviations: CT = computed tomography, EBV = Epstein-Barr virus, HCC = hepatocellular carcinoma, LPD = lymphoproliferative disorders, MRI = magnetic resonance imaging, MTX = methotrexate, PHL = primary hepatic lymphoma, RA = rheumatoid arthritis, R-CHOP = rituximab cyclophosphamide doxorubicin vincristine prednisone, SI = signal intensity, SUV_{max} = maximum standard uptake value.

Keywords: cranial neuropathy, methotrexate, primary hepatic lymphoma, rheumatoid arthritis

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1. Introduction

Rheumatoid arthritis (RA) is a chronic progressive systemic inflammatory disorder of unknown etiology that primarily involves the joints.[1] Extra-articular manifestations are also observed, including nervous system involvement. Peripheral nervous system involvement is well known, whereas cranial neuropathy is relatively rare and remains unclear.[2] Methotrexate (MTX) is the most widely used immunosuppressive drug for treating RA.[3] A relationship between lymphoproliferative disorders (LPD) such as lymphoma and MTX in RA patients has been suggested in recent reports.[4] However, the liver is rarely involved in LPD. There are only 6 reported cases of MTX-related primary hepatic lymphoma (PHL). Imaging patterns of

reported MTX-related PHL cases showed multiple or solitary nodular patterns, while there have been no reported cases of periportal infiltrating pattern.[3,5–8]

Here, we report a case of both cranial neuropathy and PHL in an RA patient. This case is also the first of MTX-related PHL showing the periportal infiltration pattern.

2. Case report

A 73-year-old woman was diagnosed with seropositive RA in 2011 (positive for rheumatoid factor and anticyclic citrullinated peptides). Her initial Disease Activity Score 28 was 5.1, indicating moderate disease activity (tender joint count, 9; swollen joint count, 9; *erythrocyte sedimentation rate*, 34 mm/h; visual analog scale score, 8). She had been treated with MTX 12.5 mg/wk for 4 years and prednisolone 5 mg/d for 2 years and then 1.25 mg/d for 2 years. Two years after receiving the RA diagnosis, she developed right diplopia. The neurologic examination results were suggestive of abducens nerve palsy, but the magnetic resonance imaging (MRI) findings were normal. She remained on the same doses of prednisolone and MTX and the diplopia improved. Thereafter, bilateral facial and oculomotor nerve palsy developed and improved intermittently for the next 2 years.

In January 2016, diplopia and left eye movement difficulty developed and cyclophosphamide therapy (625 mg) was started. MRI of the brain revealed no abnormal findings in the brain or cranial nerves. She underwent 4 cycles of therapy and the cyclophosphamide dose was increased. High-dose cyclophosphamide therapy (750–1000 mg) was started in June 2016. When she was admitted for the third cycle of high-dose cyclophosphamide in August 2016, her liver enzyme levels were elevated. The results were as follows: aspartate aminotransferase, 44 U/L; alanine aminotransferase, 55 U/L; and lactate dehydrogenase, 539 U/L. Total bilirubin and alkaline phosphatase levels were within normal limits. Other laboratory results including full blood count, inflammatory markers, liver function enzymes, serum albumin, prothrombin time–international normalized ratio, viral markers of hepatitis B and C, and tumor markers such as α-fetoprotein and carcinoembryonic antigen were normal.

A solitary 33 mm × 24 mm hypoechoic hepatic mass was detected at segment 8 on an abdominal ultrasound (Fig. 1A). On computed tomography (CT), the mass showed a well-circumscribed periportal infiltrating pattern, isoattenuation, and weak peripheral enhancement (Fig. 1B). The mass had low signal intensity (SI) on T1 and high SI on T2-weighted MRI, was weakly peripherally enhanced in the arterial phase, and had low SI in the portal and delayed phases (Fig. 1C). Its pattern was periportal

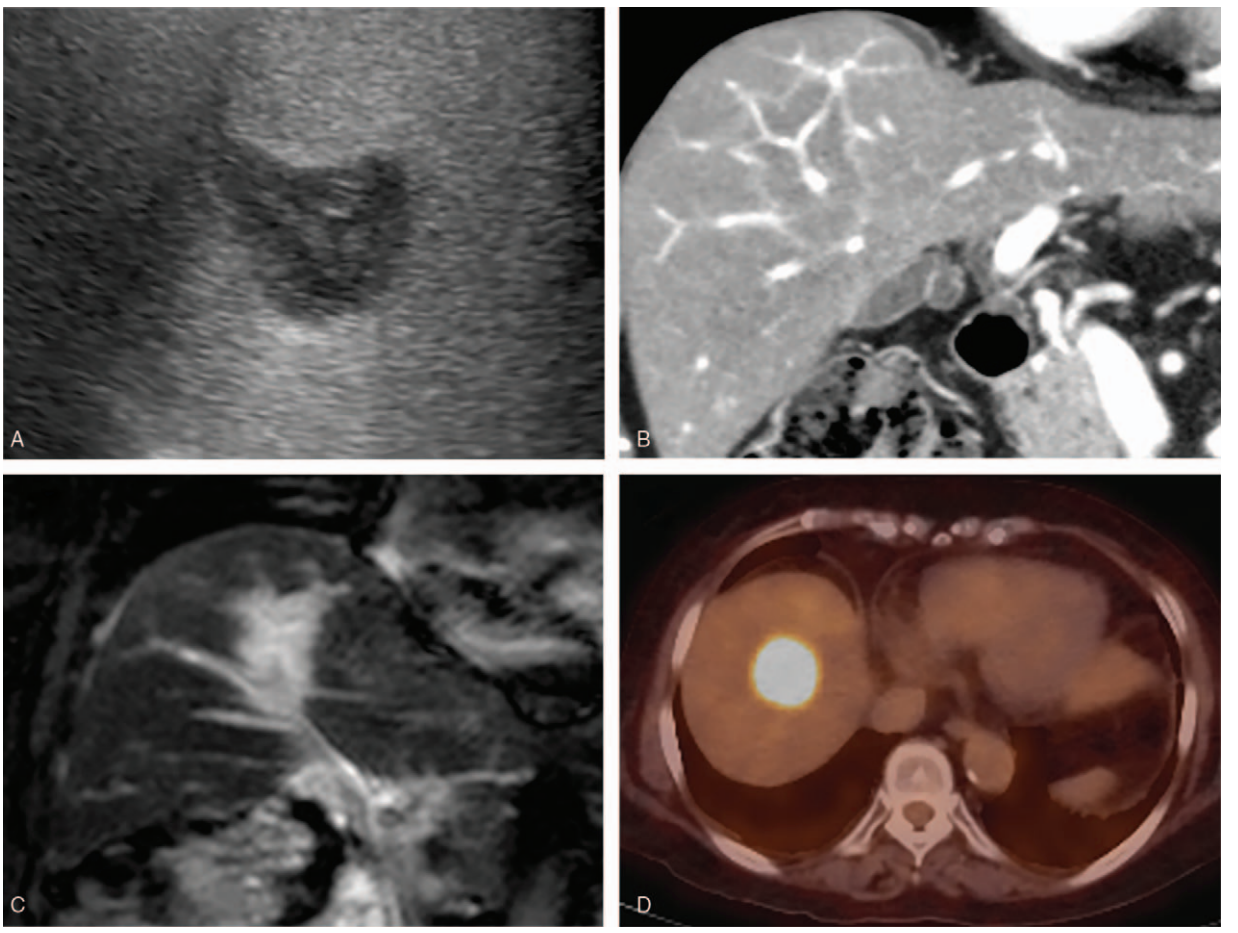

Figure 1. (A) Gray scale ultrasound image. A hypoechoic periportal infiltrating mass encases the right portal vein. (B) CT coronal image. An isoattenuated periportal infiltrating mass also encases the right portal vein. (C) Magnetic resonance image. The high signal intensity periportal mass is visible on a coronal T2-weighted image. (D) The mass shows increased SUVmax uptake on positron emission tomography. ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging.

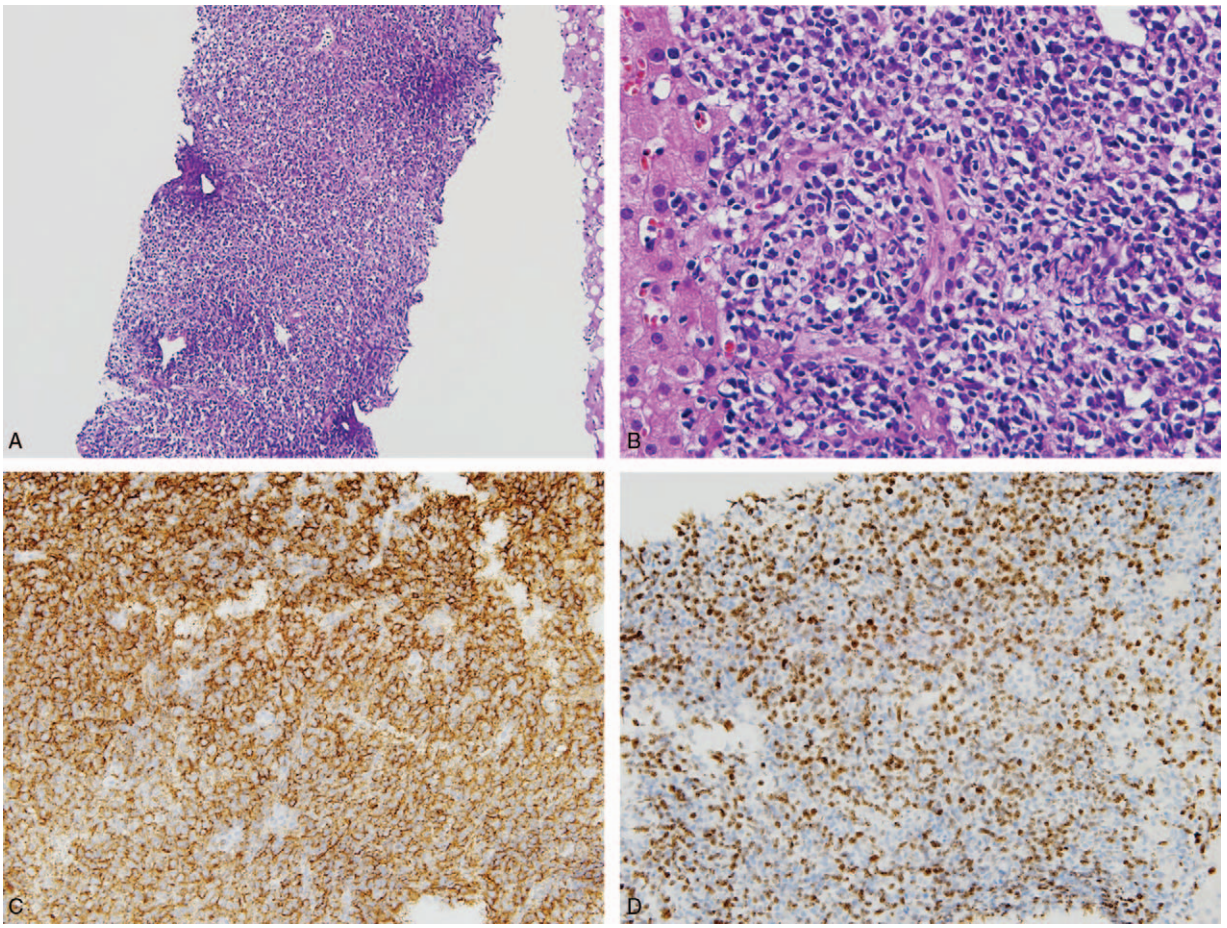

Figure 2. (A, B) Hematoxylin and eosin staining, ×200 (A) ×400 (B). The liver parenchyma has been replaced by lymphoid cells with a diffuse pattern. (C) Immunohistochemistry revealed that the tumor cells were diffusely positive for CD20. (D) The Ki-67 labeling index was approximately 80%.

infiltration. The mass had hypointense SI at the 20-minute hepatocyte phase and diffusion restriction on diffusion-weighted imaging. Positron emission tomography revealed a hypermetabolic mass with a maximum standard uptake value (SUV_{max}) of 16 (Fig. 1D). We suspected a hepatic malignancy such as hepatocellular carcinoma (HCC) or metastasis due to the diffusion restriction and increased SUV_{max} uptake. However, periportal infiltration and weakly enhancement is not a typical finding of HCC and the patient had no underlying malignancy. A diagnostic ultrasound-guided needle biopsy was performed. Hematoxylin and eosin *staining showed that* the liver parenchyma had been replaced by diffuse lymphoid cells (Fig. 2A and B). An immune histochemical analysis was positive for CD20 (Fig. 2C), Ki-67 (Fig. 2D), B-cell lymphoma (BCL)2, BCL6, and multiple myeloma oncogen-1 and negative for CD3, CD10, CD56, and Epstein-Barr virus (EBV)-encoded small RNAs by in situ hybridization. These findings were consistent with non-Hodgkin lymphoma and diffuse large BCL. Based on her history of receiving MTX for RA, she was diagnosed with other iatrogenic immunodeficiency-associated LPD according to the WHO 2008 classification of lymphoid tissue. Two weeks after the liver biopsy, a contrast-enhanced orbit MRI was performed due to aggravation of a persistent left eye movement difficulty, and the results included focal thickening with strong enhancement along the cisternal segment of the left oculomotor nerve (Fig. 3A and B).

The RA treatments that our patient was receiving, including MTX, were stopped when the PHL was diagnosed. However, after 3 weeks, the hepatic mass on CT and elevated liver enzymes persisted. Thus, she started a chemotherapy regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). After 3 cycles of R-CHOP over 3 months, the hepatic mass disappeared on CT and the liver enzyme levels normalized. The left eye movement difficulty and follow-up orbit MRI findings improved (Fig. 3C and D). The patient was treated with a total of 6 cycles of R-CHOP. No instances of relapse have occurred in 2 years of follow-up.

This study design was approved by the appropriate ethics review boards of Kyung Hee University Hospital. Informed consent was waived because only imaging findings and clinical data were retrieved from the picture archiving and communication system server and medical records.

3. Discussion

Our RA patient was diagnosed with recurrent cranial neuropathy without peripheral nerve involvement and MTX-related PHL. PHL is an extremely rare hepatic malignancy with a reported incidence of 0.4% for extra-nodal non-Hodgkin's lymphoma and 0.016% for non-Hodgkin's lymphoma.[9,10] The etiology of PHL remains unclear, although viruses such as EBV and hepatitis as well

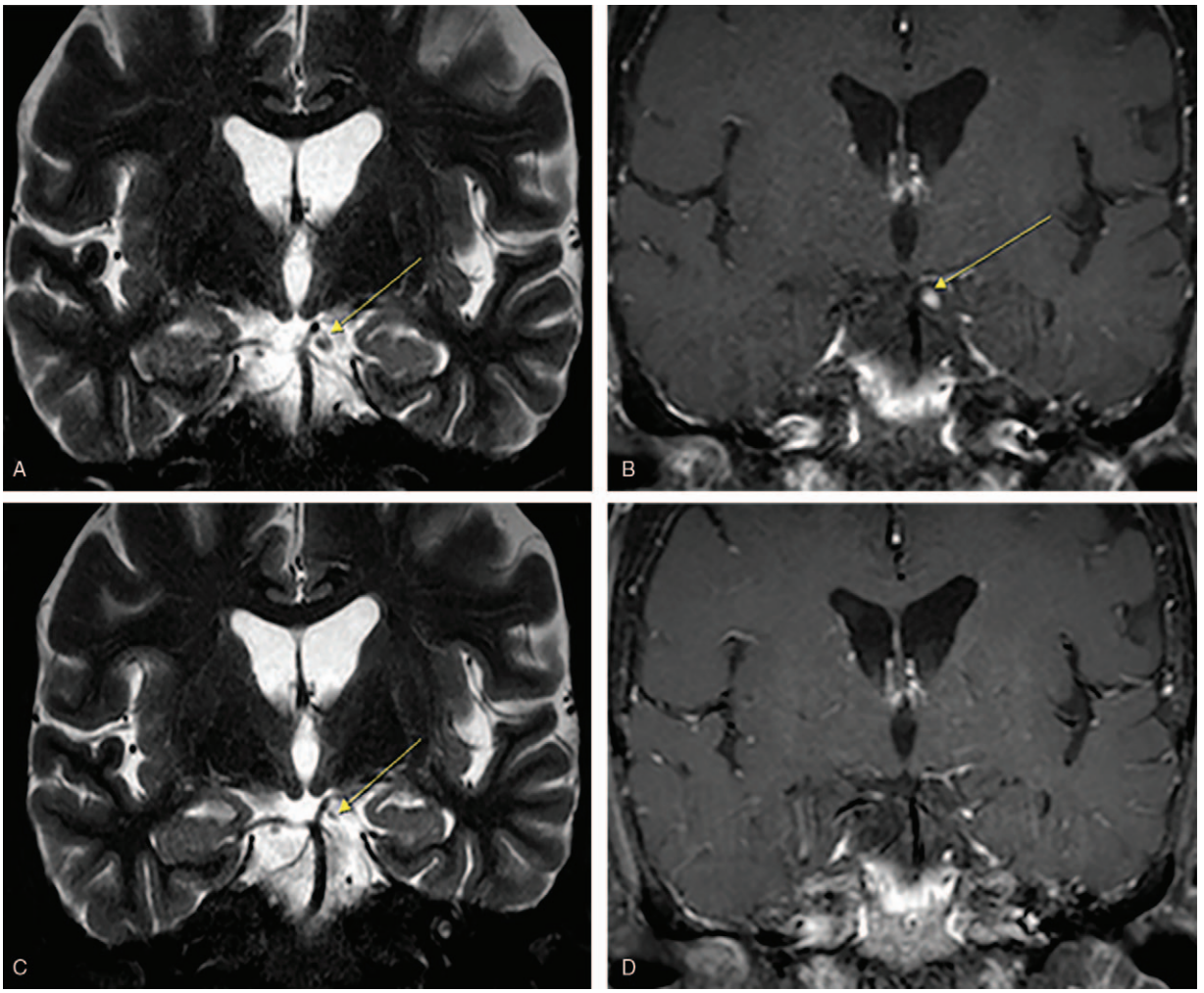

Figure 3. (A and B) The left oculomotor nerve (yellow arrow) is thickened with avid enhancement on an orbital MRI performed on September 9, 2016. (C and D) The follow-up orbital MRI performed after chemotherapy on December 6, 2016 revealved that the left oculomotor lesion had disappeared. **A and C: T2-weighted coronal image; B and D: enhanced coronal images; MRI = magnetic resonance imaging.

as immunosuppressive therapy have been implicated.[6] In this case, serologic tests for the hepatitis viruses and EBV were negative, but the patient had a long history (57 months) of receiving MTX therapy for RA. Therefore, we suspected that the MTX treatment may be correlated with the occurrence of the PHL.

The association between LPD and autoimmune disorder has been under investigation for years, and LPD is expected to be a result of a drug-induced immunosuppressive state.[3,11] Many recent reports have shown an association between MTX and LPD.[12–15] Approximately 40% of MTX-related LPD cases develop in extra-nodal sites such as the lung, kidneys, and gastrointestinal tract.[16] However, only 6 cases of MTX-related PHL have been reported.[3,5–8] Hepatic lymphoma can appear on imaging as a solitary or multiple nodular pattern with diffuse or periportal infiltration. The periportal infiltrating mass is the rarest type.[9] The 6 reported cases of MTX-related PHL were multiple or solitary nodular patterns on imaging.[3,5–8] To our knowledge, there have been no reports of MTX-related PHL with a periportal infiltrating mass.

Although we suspected that our patient had PHL, it is difficult to distinguish it from HCC or metastasis due to this lack of information. This lymphoma encases the portal vein without a mass effect due to the lack of desmoplastic reaction.[9] It is visible as periportal infiltrating hypoechoic masses on ultrasonography or as hypodense masses on CT. On MRI, it has low SI on T1 and high SI on T2-weighted images and is weakly enhanced.[9] PHL is considered an aggressive disease with poor prognosis. However, MTX-related LPD has better prognosis if diagnosed early.[5] Over half of the MTX-related LPD diseases showed regression after MTX withdrawal. Therefore, a period of careful observation awaiting spontaneous remission after MTX discontinuation is recommended for the treatment of MTX-related LPD.[5,17] In this case, we discontinued MTX for 3 weeks, but the liver enzyme levels did not improve and the hepatic mass was still visible on the CT scan. Chemotherapy was initiated, and a complete response was achieved. The early and accurate diagnosis of MTX-related PHL is essential in RA patients. Furthermore, ours is the first case of periportal infiltrating MTX-related PHL. Therefore, when a periportal infiltrating hepatic mass is found in RA patients, lymphoma should be considered a differential diagnosis.

Cranial neuropathy in RA is relatively rare compared to peripheral neuropathy.[2] Several previous studies have shown

that optic, sensory trigeminal, vestibulocochlear, and spinal accessory neuropathies are rarely seen in RA patients.[18–21] Furthermore, cranial neuropathy occurs in 5% of lymphoma patients.[22] Our patient had recurrent cranial neuropathy for >4 years (2013–2016) and several alternately involved cranial nerves (abducens, facial, and oculomotor nerves). In September 2016, left oculomotor nerve enhancement was first visible on an orbital MRI after PHL diagnosis.

There are several possible mechanisms of left oculomotor nerve lesions. The first mechanism is vasculitis. Approximately 4% of RA patients have vasculitis involving the small- and medium-size blood vessels. Vasculitis causes arterial occlusion, which leads to nerve damage.[20,23] The second mechanism is direct invasion of lymphoma or paraneoplastic neuropathy. Paraneoplastic neuropathy is the remote effect of malignancy that is mediated via the immune system.[24,25] A third possibility is infectious processes, but there was no evidence of infection in this patient.[26] In the first few years, the cranial neuropathy was considered caused by vasculitis due to RA since the symptoms improved with the maintenance of MTX and prednisolone. However, we suspected that the oculomotor nerve-enhancing lesion was caused by direct invasion of lymphoma or paraneoplastic neuropathy. The patient had more severe symptoms after receiving the diagnosis of PHL, and most enhancements seen on MRI occurred 2 weeks after the diagnosis. Her symptoms were reasonably controlled on chemotherapy and had resolved completely by January 2017 after 6 cycles. Follow-up orbital MRI after chemotherapy revealed that the lesion had disappeared. Thereafter, the patient has been under observation for 17 months without recurrence of the hepatic lymphoma and cranial neuropathy.

4. Conclusion

Cranial neuropathy is a rare complication compared with peripheral neuropathy in RA patients. PHL is also a very rare disease, and recent studies reported on the relationship between PHL and MTX. Here, we report a case of both cranial neuropathy and MTX-related PHL in an RA patient. Furthermore, ours is the first reported case of periportal infiltrating PHL in an RA patient treated with MTX. Thus, when a periportal infiltrating mass is found in RA patients, lymphoma should be considered a differential diagnosis.

Author contributions

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