Methotrexate-associated lymphoproliferative disorder with an osteolytic vertebral lesion in an elderly patient with rheumatoid arthritis: A case report

Hirata, Chihiro
Kenzaka, Tsuneaki
Akita, Hozuka

(Citation)
Journal of Clinical Pharmacy and Therapeutics,46(4):1178-1181

(Issue Date)
2021-08

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/90008434

Received: 23 January 2021 | Revised: 23 February 2021 | Accepted: 10 March 2021

DOI: 10.1111/jcpt.13415

Journal of Clinical Pharmacy and Therapeutics WILEY

CASE REPORT

Methotrexate-associated lymphoproliferative disorder with an osteolytic vertebral lesion in an elderly patient with rheumatoid arthritis: A case report

Chihiro Hirata MD[1] | Tsuneaki Kenzaka MD, PhD[1,2] | Hozuka Akita MD, PhD[1]

[1]Department of Internal Medicine, Hyogo Prefectural Tamba Medical Center, Tamba, Japan

[2]Division of Community Medicine and Career Development, Kobe University Graduate School of Medicine, Kobe, Japan

Correspondence
Tsuneaki Kenzaka, Division of Community Medicine and Career Development, Kobe University Graduate School of Medicine, 2-1-5, Arata-cho, Hyogo-ku, Kobe, Hyogo, 652-0032, Japan.
Email: smile.kenzaka@jichi.ac.jp

Funding information
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Abstract

What is known and objective: Methotrexate-associated lymphoproliferative disorder (MTX-LPD) is a rare complication that develops in patients treated with methotrexate (MTX).

Case summary: A 76-year-old male patient had been taking MTX for his rheumatoid arthritis. Computed tomography (CT) revealed masses in the liver, right adrenal gland and T6-T7 vertebra, including an osteolytic lesion. FDG-PET scan showed increased uptake in each lesion. MTX was discontinued, and CT showed complete remission of the tumours after three months. The disease course confirmed MTX-LPD diagnosis.

What is new and Conclusion: Bone lesions in LPDs mimic those of metastatic cancer. MTX-LPD should be considered in patients on MTX presenting with mass lesions.

KEYWORDS
C-reactive protein, elderly, lymphoproliferative disorder, methotrexate, rheumatoid arthritis

1 | WHAT IS KNOWN AND OBJECTIVE

Methotrexate (MTX) is an important drug for the treatment of rheumatoid arthritis. It is effective in controlling disease activity and preventing disease-related damages. Some patients taking MTX experience adverse events, such as severe myelosuppression, interstitial pneumonia and liver injury, during the treatment.[1]

A previous meta-analysis of epidemiological studies on rheumatoid arthritis reported a statistically significant association between rheumatoid arthritis and lymphoma.[1] MTX-associated lymphoproliferative disorder (MTX-LPD) is a lymphoma or lymphoid proliferation that occurs in patients that are immunosuppressed due to MTX administration. It is categorized as one of the "other iatrogenic immunodeficiency-associated LPDs" by the World Health Organization.[2] The first case was reported in 1991;[3] since then, cases of MTX-LPD have been increasingly reported in Japan. Approximately, 50% of patients with MTX-LPD present only with nodal lesions; however, others have shown extra-nodal lesions located in the gastrointestinal tract, skin and lungs.[1,4] Although a true causative relationship with the drug is demonstrated by complete or partial regression of LPD shortly after the discontinuation of the drug,[1] the mechanisms underlying the occurrence of MTX-LPD remain unclear. Here, we report a case of MTX-LPD accompanied by an osteolytic lesion, which was difficult to differentiate from metastatic cancer.

2 | CASE SUMMARY

A 76-year-old man with a history of rheumatoid arthritis presented to our hospital to evaluate elevated C-reactive protein level (6.13 mg/dl) detected during a regular check-up. He had no other complaints

and denied experiencing fever, night sweats, weight loss or arthralgia. He had been taking MTX for six years. His recent medication regimen was MTX 10 mg/wk, folate 10 mg/wk, salazosulfapyridine 1,000 mg/d and iguratimod 50 mg/d, and his disease was appropriately controlled with these drugs. He did not smoke or drink alcohol. On physical examination, the vital signs were as follows: blood pressure of 148/55 mm Hg, pulse of 85 beats/min, respiratory rate of 16 breaths/min, O_2 saturation of 100% on room air and body temperature of 36.3℃. No evidence of superficial lymphadenopathy was observed, and cardiovascular examination revealed normal findings. His lungs were clear on auscultation, and abdominal examination showed unremarkable findings, including the absence of hepatosplenomegaly. Table 1 presents the laboratory test results. The only notable laboratory test result was the elevated C-reactive protein level. Other results, including complete blood count, liver and renal function tests, serum albumin level and tumour markers, such as α-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9, were normal. Computed tomography (CT) revealed an osteolytic lesion adjacent to the T6-7 vertebrae, in addition to the masses in the liver and right adrenal gland. All masses were poorly enhanced with contrast, and fluorodeoxyglucose-positron emission tomography showed increased uptake in each lesion (Figure 1), which were initially thought to be metastatic lesions; this implies that he had only a few months to live. He requested optimal supportive care with no further evaluation. We referred him to his primary physician and advised the discontinuation of MTX, as MTX-LPD was a possibility.

Surprisingly, he was in good health at three months after MTX discontinuation, and CT showed complete remission of the tumours (Figure 2). The disease course confirmed the diagnosis of MTX-LPD. At the time of writing, which was two years since his MTX-LPD diagnosis, the patient is stable and without recurrence of the disease.

TABLE 1 Laboratory findings

Parameter	Recorded values	Standard values
White blood cells	5.59×10^9/L	$4.70–8.70 \times 10^9$/L
Haemoglobin	10.0 g/dl	13–17 g/dl
Platelets	241×10^9/L	$150–350 \times 10^9$/L
C-reactive protein	5.53 mg/dl	0–0.3 mg/dl
Albumin	3.0 g/dl	3.9–4.9 g/dl
Alanine transaminase	20 U/L	4–44 U/L
Lactate dehydrogenase	232 U/L	120–230 U/L
Blood urea nitrogen	12.2 mg/dl	8.5–20 mg/dl
Creatinine	0.62 mg/dl	0.53–1.02 mg/dl
AFP	6.1 ng/ml	1.3–8.5 ng/ml
CEA	2.0 ng/ml	0.4–5.2 ng/ml
CA19-9	6.8 U/ml	3.2–36.8 U/ml

Abbreviations: AFP, α-fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

3 | WHAT IS NEW AND CONCLUSION

We report a case of MTX-LPD accompanied by an osteolytic lesion. It is extremely rare for MTX-LPD cases to have a bone lesion. To the best of our knowledge, only two cases of MTX-LPD with bone involvement have been reported.[5,6] Considering that bone lesions of LPDs are difficult to differentiate from those of metastatic cancer; pathological examination and careful observation after the discontinuation of MTX treatment are needed.

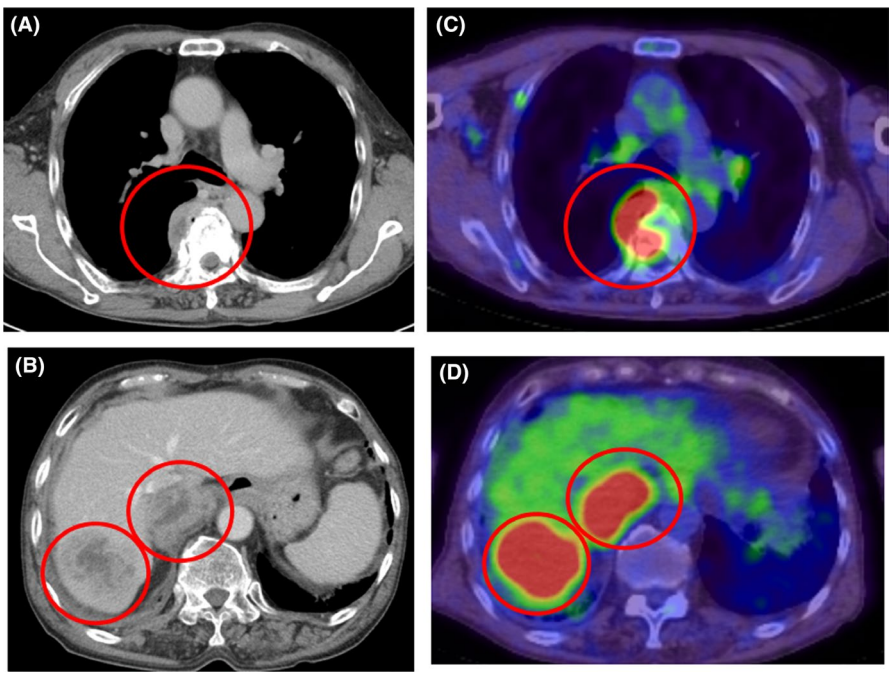

FIGURE 1 Computed tomography (CT) image. CT shows an osteolytic mass lesion adjacent to the T6-7 vertebrae (A), in addition to the masses in the liver and right adrenal gland (B) (red circles). Fluorodeoxyglucose-positron emission tomography scan showing increased uptake in each lesion (C, D) (red circles)

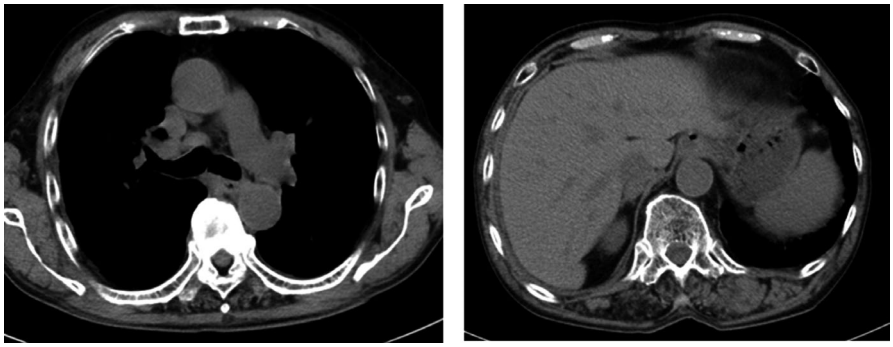

FIGURE 2 CT scans showing complete remission of the tumours at 3 months after methotrexate was discontinued

MTX-LPD is a serious complication in patients treated with MTX. As MTX is an important drug for treating rheumatoid arthritis, MTX-LPD cases have been increasingly reported in Japan. Although the mechanism underlying the disease is unknown, immunodeficiency resulting from rheumatoid arthritis combined with the immunosuppressive effect of MTX has been implicated in the pathogenesis.[4] This patient had been taking iguratimod, MTX and salazosulfapyridine. Iguratimod is a disease-modifying antirheumatic drug (DMARD) developed in Japan and is considered to elicit immunomodulatory effects by reducing the production of inflammatory cytokines, including interleukin-1β (Il-1β), Il-6, Il-8, Il-10, tumour necrosis factor α, and interferon γ, and immunoglobulin by B lymphocytes.[7] A combined therapy of iguratimod with other DMARDs is expected to be useful, especially in patients with rheumatoid arthritis who are non-responsive to MTX therapy alone.[8]

Patients with rheumatoid arthritis reportedly have a 2.0–5.5-fold higher risk of developing LPDs than the general population.[1,9]

The clinical symptoms of MTX-LPD include weight loss, fever and swelling of the superficial lymph nodes. Blood tests reveal high levels of C-reactive protein, lactate dehydrogenase or soluble-interleukin 2 receptor.[5] MTX-LPD may affect lymph nodal or extra-nodal sites, including the pharynx, liver, gastrointestinal tract, kidneys, lungs, skin and soft tissues. Approximately, 40–70% of MTX-LPD patients with rheumatoid arthritis have extra-nodal lesions.[1] According to a report of 27 cases by Yoshihara, more than half of the cases were located in the extra-nodal sites.[10] However, bone involvement is extremely rare, with only two cases having been reported to date. Oebisu et al. reported a case of MTX-LPD with a pathological fracture of the femur,[5] and Kikuchi reported a case accompanied by a spinal lesion.[6] In addition, hepatic lesions rarely develop in patients with MTX-LPD, with only 11 cases having been reported in the English literature to date.[11]

In this case, the patient had a vertebral osteolytic tumour, rendering it difficult to differentiate the tumour from metastatic cancer, thereby leading to an incorrect prognostic prediction. The radiographs of patients with LPDs typically show permeative bone destruction accompanied by extraosseous soft-tissue masses. It is difficult to differentiate LPDs from metastatic cancer, leukaemia or small round-cell tumours, such as an Ewing's sarcoma, by radiographic findings.[12,13] Therefore, a thorough pathological examination should be performed. In this case, the patient refused to undergo a biopsy; thus, a diagnosis was established based on the patient's clinical course.

A remarkable response to MTX cessation is helpful for the diagnosis of MTX-LPD.[1] Spontaneous resolution of LPD after the withdrawal of MTX is reported in 20–73% of patients.[1] Otherwise, LPDs regrow after the initial regression in some patients and require chemotherapy, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone).[9] Our case showed complete remission of all the tumours in the liver, right adrenal gland and T6-7 vertebra, and the disease course confirmed the diagnosis. Discontinuation of MTX and careful follow-up can contribute to accurate diagnosis, especially if the patient does not want to undergo a pathological examination, or it is technically difficult to perform a biopsy. When a patient taking MTX presents with mass lesions and development of LPD is suspected, initial cessation of MTX has a diagnostic and therapeutic value.

In conclusion, our findings indicate that bone lesions in LPDs mimic those of metastatic cancer. Therefore, MTX-LPD should be considered in patients on MTX who present with mass lesions.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

PATIENT CONSENT STATEMENT

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

ORCID

Tsuneaki Kenzaka https://orcid.org/0000-0002-3120-6605

REFERENCES

1. Harigai M. Lymphoproliferative disorders in patients with rheumatoid arthritis in the era of widespread use of methotrexate: a review of the literature and current perspective. *Mod Rheumatol*. 2018;28:1-8.
2. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*, 4th edn. Lyon: IARC; 2008:335-351.
3. Shiroky JB, Frost A, Skelton JD, Haegert DG, Newkirk MM, Neville C. Complications of immunosuppression associated with weekly low dose methotrexate. *J Rheumatol*. 1991;18:1172-1175.
4. Mariette X, Cazals-Hatem D, Warszawki J, et al. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood*. 2002;99:3909-3915.
5. Oebisu N, Hoshi M, Ieguchi M, et al. Lymphoproliferative disorder with pathological fracture of the femur in a patient with rheumatoid

arthritis treated with methotrexate: a case report. *Mol Clin Oncol*. 2018;9:187-191.
6. Kikuchi N, Uesugi M, Koda M, et al. Methotrexate-related lymphproliferative disorder of the lumber spine origin presenting with severe low-back pain: case report. *J Neurosurg Spine*. 2018;29:545-548.
7. Lu LJ, Bao CD, Dai M, et al. Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. *Arthritis Rheum*. 2009;61:979-987.
8. Li J, Bao J, Zeng J, et al. Iguratimod: a valuable remedy from Asia Pacific region for ameliorating autoimmune diseases and protecting bone physiology. *Bone Res*. 2019;7:27.
9. Hashimoto K, Akagi M. Lymphoproliferative disorder in an elderly rheumatoid arthritis patient after longterm oral methotrexate administration: a case report. *Mol Clin Oncol*. 2018;9:293-296.
10. Yoshihara R, Uefuji A, Murata M, Nakagawa N, Tanaka Y, Shiozawa K. Clinical manifestation of twenty-seven cases of methotrexate-associated lymphoproliferative disorders. *Clin Rheumatol Rel Res*. 2017;29:164-172.
11. Ono R, Kumagae T, Uojima H, et al. Hepatic methotrexate-associated lymphoproliferative disorders identified by multiple liver tumors: a case report and review of the literature. *J Med Case Rep*. 2019;13:196.
12. Braunstein EM, White SJ. Non-Hodgkin lymphoma of bone. *Radiology*. 1980;135:59-63.
13. Gabel GT, Sim FH, Beabout JW, Haberman TM, Wold LE. Non-Hodgkin's lymphoma of bone. *Orthopedics*. 1989;12:1139-1142.

How to cite this article: Hirata C, Kenzaka T, Akita H. Methotrexate-associated lymphoproliferative disorder with an osteolytic vertebral lesion in an elderly patient with rheumatoid arthritis: A case report. *J Clin Pharm Ther*. 2021;46:1178–1181. https://doi.org/10.1111/jcpt.13415