Endocrinology, Diabetes & Metabolism CASE REPORTS

M Aoshima and others | MTX–LPD with hypopituitarism

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Methotrexate-associated lymphoproliferative disorder with hypopituitarism and central diabetes insipidus

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Summary

Patients treated with immunosuppressive drugs, especially methotrexate (MTX), rarely develop lymphoproliferative disorders (LPDs), known as MTX-related LPD (MTX–LPD). The primary site of MTX–LPD is often extranodal. This is the first reported case of MTX–LPD in the pituitary. A 65-year-old woman was admitted to our hospital with symptoms of oculomotor nerve palsy and multiple subcutaneous nodules. She had been treated with MTX for 11 years for rheumatoid arthritis. Computed tomography showed multiple masses in the orbit, sinuses, lung fields, anterior mediastinum, kidney, and subcutaneous tissue. Brain magnetic resonance imaging revealed a sellar mass. She was diagnosed with hypopituitarism and central diabetes insipidus based on endocrine examination. Although pituitary biopsy could not be performed, we concluded that the pituitary lesion was from MTX–LPD, similar to the lesions in the sinuses, anterior mediastinum, and subcutaneous tissue, which showed polymorphic LPD on biopsy. MTX was discontinued, and methylprednisolone was administered to improve the neurologic symptoms. After several weeks, there was marked improvement of all lesions, including the pituitary lesion, but the pituitary function did not improve. When pituitary lesions are caused by MTX–LPD, the possibility of anterior hypopituitarism and central diabetes insipidus needs to be considered. Further studies are needed to investigate the effectiveness of early diagnosis and treatment of MTX–LPD in restoring pituitary dysfunction.

Learning points

- Pituitary lesions from MTX–LPD may cause hypopituitarism and central diabetes insipidus.
- Pituitary metastasis of malignant lymphoma and primary pituitary lymphoma, which have the same tissue types with MTX–LPD, have poor prognosis, but the lesions of MTX–LPD can regress only after MTX discontinuation.
- In cases of pituitary lesions alone, a diagnosis of MTX–LPD may be difficult, unless pituitary biopsy is performed. This possibility should be considered in patients treated with immunosuppressive drugs.
- Pituitary hypofunction and diabetes insipidus may persist, even after regression of the lesions on imaging due to MTX discontinuation.

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Background

Methotrexate (MTX) is the main immunosuppressant drug for autoimmune diseases, particularly in rheumatoid arthritis (RA) (1). Lymphoproliferative diseases had been shown to occur in some patients treated with MTX. This condition had been called MTX-related lymphoproliferative disease (MTX–LPD) and was categorized as other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA–LPDs) and defined as immunodeficiency-associated lymphoma in the fourth edition of the World Health Organization classification (2). MTX–LPD had been associated with Epstein–Barr virus (EBV) positivity, similar to human immunodeficiency virus-associated LPD and posttransplant LPD (3).

A major feature in about half of MTX–LPD cases was restoration of normal immunity, resulting in spontaneous resolution of lesions, upon discontinuation of MTX (4). For lesions that do not resolve by MTX discontinuation alone, immunotherapy and chemotherapy had been necessary (5). The common primary sites of MTX–LPD had been reported to be the extranodal areas throughout the body (6). To the best of our knowledge, this was the first report on MTX–LPD in the pituitary gland.

Case presentation

A 65-year-old woman presented with headache, right ophthalmalgia, and right facial dysesthesia for 3 months. She was admitted to our hospital because of oculomotor nerve palsy and the development of 1 cm subcutaneous nodules on the upper arm, anterior chest, and ankles for 2 weeks. She had been treated with MTX plus prednisolone for 11 years for RA. The latest doses were 8 mg/week of MTX and 5 mg/day of prednisolone, and the total dose of MTX was 4540 mg. She was previously administered disease-modifying antirheumatic drugs, such as azulfidine and abatacept and had been treated with iguratimod 2 years ago. High-dose prednisone was started 2 years ago because she suffered from RA-associated interstitial lung disease.

Physical examination showed right eyelid ptosis, external dislocation, and mydriasis. She had no superficial lymphadenopathy.

Investigation

Computed tomography (CT) showed splenomegaly and multiple masses in the right orbit, right posterior ethmoid sinus, left sphenoidal sinus, both lungs, anterior mediastinum, right kidney, and subcutaneous tissue (Fig. 1A). Laboratory findings (Table 1) showed high levels of lactate dehydrogenase, soluble interleukin-2 receptor, C-reactive protein, and Epstein–Barr virus DNA; anti-SS antibody, anti-neutrophil cytoplasmic antibody, and interferon gamma-release assay were negative. In addition, the low thyroid-stimulating hormone (TSH), free triiodothyronine (FT-3), and free thyroxine (F-T4) levels led us to perform endocrine evaluation.

Further endocrine examination showed hypopituitarism, without growth hormone (GH) deficiency. A hypotonic saline infusion test and DDAVP test confirmed the diagnosis of central diabetes insipidus (CDI). Brain magnetic resonance imaging (MRI) revealed a 2.2-cm-wide and 1.6-cm-tall sellar mass, which invaded the right cavernous sinus and compressed the superior surface of the pituitary stalk. The high-signal intensity in the posterior pituitary lobe disappeared on T_1-weighted MRI (Fig. 1C).

Treatment

The causative drug MTX was discontinued, and then performed biopsies from the sinus, anterior mediastinum, lung, and subcutaneous tissue. We initially administered methylprednisolone pulse therapy (250 mg for 5 days) to improve oculomotor nerve palsy, which was progressing rapidly.

Biopsies from the lesions in the sinuses, anterior mediastinum, and subcutaneous tissue revealed proliferation of small- and medium-sized atypical lymphocytes and a portion of necrotic tissue (Fig. 2A and 2B). The atypical lymphoid cells were positive for CD20 (Fig. 2C), CD79α (Fig. 2D), and CD30 but were negative for CD5, CD10, and cyclin D1. *In situ* hybridization showed Epstein–Barr virus-encoded ribonucleic acid in the cell nuclei (Fig. 2E). These pathological findings and medical history led to a diagnosis of a polymorphic LPD (P–LPD) type of MTX–LPD. In addition, there were no significant findings on flow cytometry and chromosome banding, which could have been useful adjuncts to the diagnosis (7).

And she was started on thyroxine and desmopressin replacement, in addition to prednisolone 5 mg and subjectively improved.

Outcome and follow-up

On serial CT scan, the multiple lesions did not regress immediately, but they were gradually reduced after more

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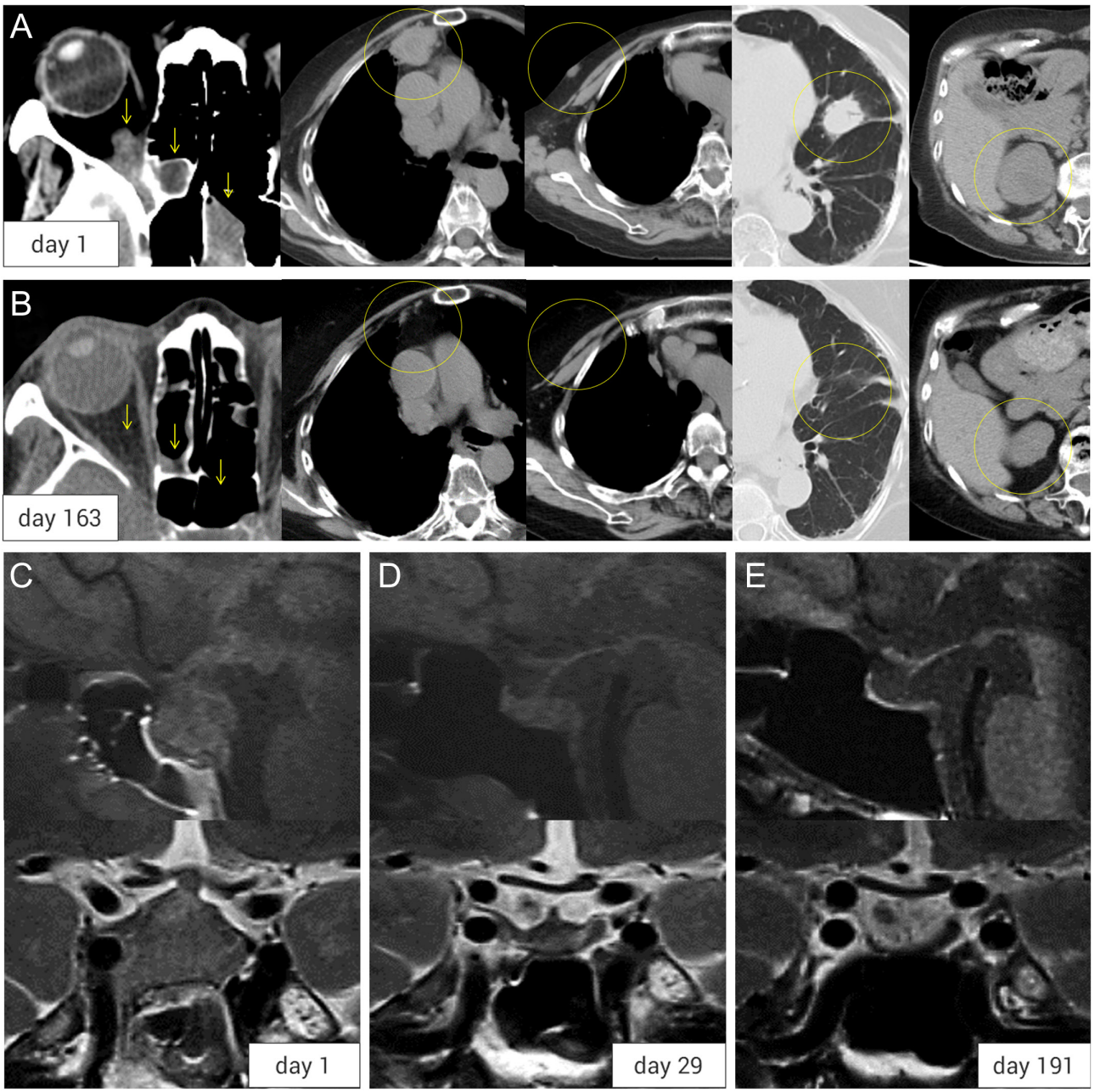

Figure 1
(A) Computed tomography showed the multiple masses in orbit, sinuses, lung fields, anterior mediastinum, kidney, subcutaneous tissue. (B) Almost all of the lesions regressed after 5 months of MTX discontinuation. (C) Brain magnetic resonance imaging (MRI) of pituitary gland revealed a 2.2-cm-wide and 1.6-cm-tall sellar mass. (D) Three weeks later, MRI revealed remarkable regression of the sellar mass. (E) Six months later, MRI showed an empty sella.

than 1 week of treatment, which was 2 weeks after MTX discontinuation. Three weeks later, repeat MRI of the pituitary gland revealed remarkable regression of the sellar mass (Fig. 1D). Although we could not perform pituitary biopsy, the seller mass, similar to the other lesions, was suspected to be MTX–LPD, based on these clinical findings. After 1 month, the neurologic deficits gradually improved.

Ultimately, almost all of the lesions regressed after 5 months of MTX discontinuation (Fig. 1B). Because the pituitary lesion improved on imaging, we repeated endocrine evaluation at three months after MTX discontinuation and found persistently high prolactin (PRL) levels. Furthermore, both hypopituitarism (Table 1) and CDI did not improve. Therefore, hormone replacement therapy was continued. Six months later,

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Table 1 Laboratory data and results from endocrinological and immunological tests on admission (day 6) and with disease progression (day 106).

Investigations	Units	Values (day 6)	Values (day 106)	Reference range
White blood cells	$\times 10^3/\mu L$	6.95		3.5–9.1
Hemoglobin	g/dL	13.2		11.3–15.2
Platelet	$\times 10^3/\mu L$	297		130–369
Na	mEq/L	137.5		135–147
K	mEq/L	4.6		3.5–5.5
Cl	mEq/L	98.4		98–108
Creatinine	mg/dL	1.51		0.4–0.8
Lactate dehydrogenase	U/L	383		106–211
Albumin	g/dL	3.7		3.9–4.9
C-reactive protein	mg/dL	2.04		<0.27
Rheumatoid factor	U/mL	13		0–15
Matrix metalloproteinase-3	ng/mL	133.5		16.1–56.8
Anti-citrullinated protein antibody	IU/mL	92.1		0–4.4
Soluble interleukin-2 receptor	U/mL	2150		145–519
Epstein–Barr virus DNA	copy/mL	1600		<20
Krebs von den Lungen-6	U/mL	1140		<500
Surfactant protein-D	ng/mL	34.7		<110
Immunoglobulin G4	mg/dL	40.8		4.5–117.0
Anti-thyroglobulin antibody	IU/mL	67		<28
Anti-thyroid peroxidase antibody	IU/mL	12		<16
Antidiuretic hormone	pg/mL	0.6		<2.8
Serum osmolality	mOsmol/kg	302		270–295
Urine osmolality	mOsmol/kg	167		>300
FSH	mIU/mL	0.68	0.1	26.2–113.3 (menopause)
LH	mIU/mL	<0.1	<0.1	8.7–39.0 (menopause)
Prolactin	ng/mL	72.43	93.33	4.91–29.3
TSH	μIU/mL	0.656	0.023	0.50–5.00
FT-3	pg/mL	0.93	–	2.30–4.00
FT-4	ng/dL	0.4	–	0.90–1.70
ACTH	pg/mL	5	<2.0	7.2–63.3
Cortisol	pg/mL	1.8	1	7.1–19.6
GH	ng/mL	0.55	0.4	0.13–9.88
IGF-1	ng/mL	69	43	64–188 (65-year-old woman)

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT-3, free triiodothyronine; FT-4, free thyroxine; GH, growth hormone; IGF1, insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

repeat MRI of the pituitary grand showed an empty sella (Fig. 1E).

Discussion

MTX–LPD is a rare disease (8), which had been reported since 1991 as OIIA–LPDs caused by MTX administration (9, 10). The histopathologic types of MTX–LPD vary, but they have common features with sporadic LPD, as the tendency for diffuse large B-cell lymphoma (DLBCL) to account for 60% and Hodgkin lymphoma to account for 20% had been consistently reported in previous studies (11). The frequency of P–LPD, which was the pathologic subtype in this case, differed among reports (2, 12, 13). Tsukui *et al*. reported that P–LPD was associated with a better clinical course, even when compared with the other tissue types of MTX–LPD (12). Half of the sites of MTX–LPD are in the extranodal areas throughout the body and are versatile. However, as far as we searched, there had been no report on MTX–LPD in the orbital area, which was seen in this present case (5). Central nervous lesions were reported in eight cases and were in various sites (e.g., cerebellum, medulla oblongata, subdural, and so forth), except in the pituitary (14, 15, 16, 17, 18, 19). Although we were not able to histopathologically confirm the MTX–LPD etiology of the pituitary lesion in this case, the pathologic background of pituitary lesion and the other lesions were likely the same because the same pathologic subtype had been reported in biopsy specimens of the other lesions and the pituitary lesion developed simultaneously with the other lesions.

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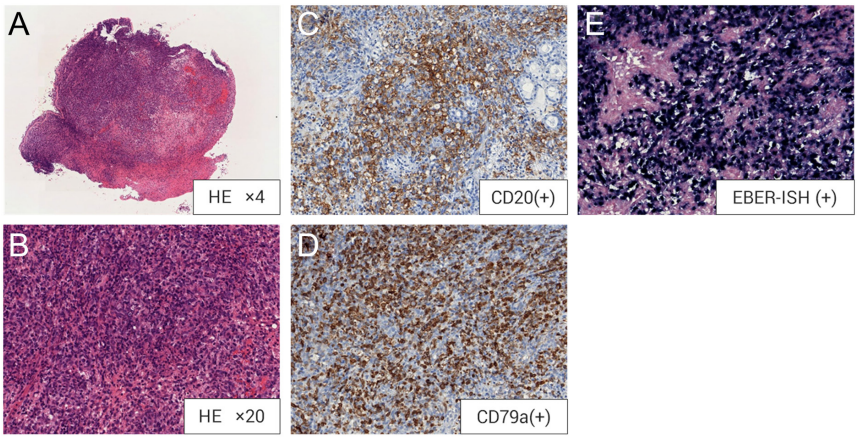

Figure 2
(A) Hematoxylin and eosin stain (4× original magnification). (B) (20× original magnification). Small or medium-sized atypical lymphoid cells with necrosis. There are no findings of granuloma or fibrosis. (C, D and E) Lymphoma cells were positive for CD20, CD79a and Epstein–Barr encoding region (EBER).

Diseases that exhibit pituitary gland structural disorders and hypopituitarism mainly include adenomas, primary or metastatic neoplasms, granulosa lesions, and inflammatory lesions. Pituitary metastases comprised only 1–5% of sellar mass lesions (20). Furthermore, the incidence of lymphoma was 0.5% among malignant pituitary metastases (21). In addition, primary pituitary lymphoma (PPL) is quite rare, and pituitary adenoma is the most common cause of hypopituitarism (22). The clinical symptoms associated with pituitary adenoma gradually occur because of the relatively slow tumor growth. However, the symptoms in this case appeared suddenly. Although GH and gonadal function are usually the first to be affected in hypopituitarism due to pituitary adenoma, GH response was initially preserved in this case. The high level of PRL was thought to have been due to stalk disturbance, but it did not decrease with tumor regression. On the other hand, the right eye neuropathy improved with reduction of the tumor mass. These suggested that different mechanisms may be involved.

Autoimmune hypophysitis (AH) is consistent with MTX–LPD, in terms of lymphocyte proliferation in the pituitary gland. From the results discussed earlier, we examined the mechanism of hypopituitarism in this case, based on these diseases. Patients with pituitary metastasis of lymphoma usually present with CDI, secondary to a lesion in the posterior lobe. (23) In previous reviews of 30 cases, both anterior lobe dysfunction (70%) and diabetes insipidus (36%) were more frequent in PPL than in pituitary adenoma (24, 25).

Even in patients with PPL and pituitary metastasis of lymphoma, chemotherapy and radiotherapy may be administered, but most reports did not describe the pituitary function after treatment because of the poor prognosis. Most cases of pituitary metastasis of lymphoma were reported to have irreversible hormonal dysfunction (26, 27). Siew *et al.* reported that six of eight lymphoma cases with hypopituitarism had partial and complete pituitary function improvement after chemotherapy (20). As far as we searched, reports on pituitary function improvement after chemotherapy, especially for intravascular large B-cell lymphoma (IVLBCL), were notable.

Sawada *et al.* suggested that hypopituitarism due to IVLBCL was induced by lymphoid cell infiltration into an angiogenic-rich pituitary vasculature (28). Interestingly, some reports on pituitary function improvement after chemotherapy showed abnormal pituitary gland accumulation on positron emission tomography (PET) scan but no pituitary lesion on MRI (29, 30). This confirmed the fact that hypopituitarism is not merely due to physical expansion of the tumor but to the diffuse lymphoma cell infiltration and AH (31). PET-scan is more important in cases with hypopituitarism that present with macroscopically normal pituitary gland. Although PET-CT was not performed in this case, it had been shown in some reports to aid in the diagnostic and therapeutic effect determination of hypopituitarism (32).

Only few studies have reported on the recovery of hypopituitarism after successful chemotherapy, even in advanced cases. Nakashima *et al.* reported recovery of pituitary function and resolution of a pituitary lesion, which had been completely replaced by abnormal DLBCL lymphocytes, after chemotherapy (33). Another report by Sandra *et al.* showed slow but full recovery of pituitary function at 2 years after achieving hematologic remission in a case of pituitary lesion from IVLBCL, despite a partially empty sella; they suggested that immunochemotherapy recovered the vascular infiltration of the lymphoma cells (31). In most cases of pituitary lymphoma, MRI reveals pituitary enlargement, normal-sized and atrophic pituitary, or empty sella. These had been thought to

represent a later disease stage (33). Consequently, in any of these cases, spontaneous remission can occur by a small amount of undisturbed normal pituitary tissue compensating for the pituitary function.

AH differs from MTX–LPD, in terms of the inflammatory diseases in which heteromorphic lymphocytes proliferate, but it had been the more common disease exhibiting hypopituitarism. In AH, direct pituitary acinar cell disorder due to autoimmune mechanism is presumed to cause the pituitary dysfunction, and steroids are often used. Steroids in combination with chemotherapy are a common choice of treatment in patients with orbital lymphoma (34). Reports on lymphoma, such as central nervous system primary lymph granulosa; pituitary metastasis of malignant lymphoma; and PPL showed the positive effects of steroids on pituitary function improvement (28, 35, 36). In this case, although the orbital lesion did not regress immediately after high-dose steroid administration, we confirmed the reduction of the lesion 1 week later. We could not accurately determine the effect of steroids on this patient's pituitary lesion because MTX discontinuation had been associated with tumor shrinkage within 1–2 weeks, based on several cases that were previously reported, and after 3 weeks, as seen on repeat MRI evaluation in this case. Moreover, we considered that the pituitary function did not improve after steroid treatment, because the pituitary cells may have been irreversibly damaged, as what was observed pathologically in the other necrotic lesions. Even in AH, in which fibrosis or destruction has progressed, improvement of pituitary function by steroids cannot be expected. In this case, MTX was discontinued about 3 months after the onset of symptoms, but her pituitary function did not improve. Therefore, early diagnosis is desired because MTX discontinuation at an early stage may hasten the recovery of pituitary function.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

All authors were involved in the preparation and writing of the manuscript.

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