CASE REPORT

Mycophenolate mofetil treatment in a patient with recurrent lymphocytic hypophysitis

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SUMMARY

Lymphocytic hypophysitis (LHP) is a relatively rare disease characterised by lymphocytic infiltration of the pituitary gland, resulting in pituitary dysfunction. LHP is generally responsive to corticosteroid therapy, but cases with recurrence require clinicians to select second-line therapy. We report here the case of a 58-year-old patient with LHP who developed panhypopituitarism and bitemporal hemianopia. He responded to prednisolone 40 mg/day but relapsed during tapering. The prednisolone dose was increased again and mycophenolate mofetil (MMF) was added. Thereafter, over the course of 1 year, prednisolone was tapered to 8 mg/day without relapse. Because of the rarity of LHP, there are no standard treatment protocols that support the choice of a specific immunosuppressive drug. MMF was effective for recurrent LHP in our case. Further accumulation of cases is needed to establish the standard treatment for this disease.

BACKGROUND

Lymphocytic hypophysitis (LHP) is an uncommon disorder characterised by autoimmune inflammation of the pituitary gland.[1] It causes functional impairment of pituitary hormone secretion, leading to hypopituitarism and diabetes insipidus. High-dose corticosteroid therapy is reported to be effective in inducing remission of the disease by treating both the pituitary dysfunction and compression symptoms.[2] However, the disease recurs during tapering in some patients with LHP.[3 4] Immunosuppressive drugs would be required in anticipation of steroid-sparing effects for such patients. Because of the rarity of LHP, there are no standard evidence-based treatment guidelines that support the choice of a specific immunosuppressive drug. Further accumulation of cases is therefore needed to establish the treatment standard.

Mycophenolate mofetil (MMF) is an immunosuppressive agent originally used in solid organ transplantation,[5] and it now plays an increasing role in the treatment of various autoimmune diseases.[6] We describe here a Japanese man with LHP that recurred after successful corticosteroid monotherapy and who was effectively treated with MMF.

CASE PRESENTATION

A 58-year-old Japanese man was referred to our clinic in September 2015 with a 3-month history of generalised fatigue, low-grade fever and skin rash. He complained that he had lost 18 lbs (8 kg) of his total body weight in the previous 2 months. On examination, his weight was 182 lbs (83 kg), body temperature 37.3°C, blood pressure 123/75 mm Hg and pulse rate 87 beats/min. Physical examination of the chest and abdomen was unremarkable. He exhibited mild proximal muscle weakness in the lower extremities. The right wrist was swollen and tender. Skin examination revealed an itchy, dry and scaly rash over his arms, legs and face.

INVESTIGATIONS

Laboratory investigations showed C-reactive protein of 2.7 mg/L, haemoglobin of 13.5 g/dL, white blood cell count of 4.5×10^9/L (neutrophils 1.5×10^9/L, lymphocytes 2.2×10^9/L, eosinophils 0.4×10^9/L) and platelet count of 226×10^9/L. Serum creatine kinase and lactate dehydrogenase levels were slightly elevated at 393 U/L (normal 41–153) and 238 U/L (124–222), respectively. Serum total IgG, IgA, IgM and IgG4 were not elevated (1079 mg/dL, 311 mg/dL, 46 mg/dL and 12 mg/dL, respectively). Immunological investigations showed that he was negative for Hep-2 antinuclear antibody. Serum complement concentration was normal. Urinalysis was negative for proteinuria and occult blood. Chest X-ray was also normal. Electromyogram revealed a myogenic pattern in the proximal muscles.

Thyroid function tests showed thyroid stimulating hormone of 0.71 µIU/mL (normal 0.4–6.0) and free thyroxine of <0.40 µIU/mL (normal 4.5–21.1). Further hormonal examination revealed hypopituitarism as follows: luteinising hormone <0.1 mIU/mL (normal 0.7–5.72), follicle-stimulating hormone 0.5 mIU/L (normal 1.0–12.0), adrenocorticotropic hormone 17.3 pg/mL (normal 7.2–63.3)and cortisol 0.3 µg/mL (normal 4.5–21.1). Gadolinium-enhanced MRI showed homogeneous enhancement of the pituitary gland with an enlarged stalk and a cystic suprasellar mass with enhanced wall thickness (figure 1A). The characteristic posterior pituitary bright spot was absent. Although he did not notice visual disturbance, a visual acuity test revealed bitemporal hemianopia. Pituitary gland biopsy was not performed because the patient declined. The provisional diagnosis was LHP.

TREATMENT

The patient was treated with intravenous steroid pulse therapy (methylprednisolone 1 g/day for 3 days) followed by oral prednisolone at 40 mg/day; thyroid hormone replacement therapy was also started. He responded to the corticosteroid

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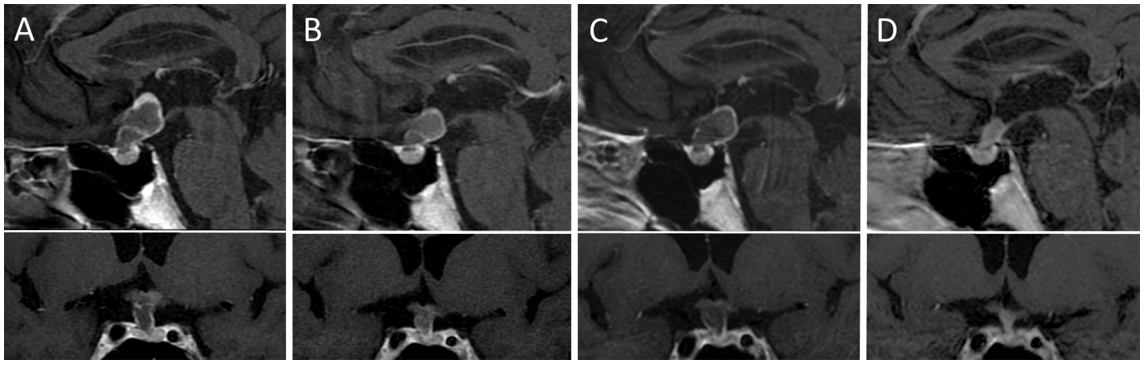

Figure 1 Gadolinium-enhanced sagittal (upper) and coronal (lower) T1 MRI before (A) and at 1 month (B) and 3 months (C) after starting initial corticosteroid therapy. Homogenously enhanced pituitary gland, enlarged stalk and cystic suprasellar mass with enhanced wall thickness seen before treatment show some resolution 1 month after starting treatment but recurrence at 3 months. Six months after starting combination therapy with corticosteroid and mycophenolate mofetil, the pituitary stalk and suprasellar mass are markedly reduced in size (D).

treatment and the generalised fatigue dramatically resolved. One week later, he developed polyuria. We presumed that diabetes insipidus was masked by corticosteroid deficiency due to hypopituitarism. We then started treatment with nasal administration of 1-desamino-8-d-arginine vasopressin (DDAVP) and the polyuria was subsequently well controlled. One month later, the pituitary mass evaluated on MRI showed some reduction in size (figure 1B), and the visual acuity improved. Consequently, the steroid dose was gradually tapered.

However, in December 2015 (3 months after starting initial therapy), he presented with recurrence of visual disturbance while still taking prednisolone 13 mg/day. MRI showed that the pituitary mass had enlarged in size (figure 1C). The dose of prednisolone was increased to 40 mg/day. Also, we considered the option of immunotherapy with off-label use of MMF to avoid further recurrence of the disease. We obtained written informed consent from the patient and MMF 1 g/day was added to the steroid therapy. One month later, the dose of MMF was increased to 2 g/day. The patient received 40 mg/day of prednisolone for 2 weeks, followed by 30 mg/day for 4 weeks, 25 mg/day for 3 weeks, 20 mg/day for 3 weeks, 17.5 mg/day for 4 weeks, after which the drug was gradually tapered. He had some of the glucocorticoid-induced side effects including obesity and increased intraocular pressure.

OUTCOME AND FOLLOW-UP

Visual acuity was restored by combination treatment with MMF and the increased dose of prednisolone. Follow-up MRI showed that the pituitary stalk and suprasellar mass had markedly reduced in size (figure 1D). In January 2017 (13 months after starting co-administration of MMF), prednisolone was successfully tapered to 8 mg/day without any recurrence of the disease. The patient was clinically well, although he continued to receive thyroid hormone replacement therapy and intranasal DDAVP. Currently, his condition is being monitored meticulously and continuously to promptly detect relapse of LHP.

DISCUSSION

A definitive diagnosis of LHP can be made only by pathological examination of pituitary biopsy obtained at surgery. In many cases, however, non-invasive imaging studies such as MRI can contribute to the diagnosis, thus reducing the need for surgical procedures, as in our case. Differential diagnoses to consider aside from LHP include pituitary adenoma, craniopharyngioma, inflammatory granuloma and cyst.[7] Pituitary adenoma is the most common. MRI features typically indicative of LHP are symmetric enlargement of the pituitary gland, thickened pituitary stalk and the absence of the posterior pituitary bright spot.[7] In our patient, after gadolinium administration, T1-weighted images revealed homogeneous enhancement of the pituitary gland with an enlarged stalk and a cystic suprasellar mass with enhanced wall thickness. The posterior pituitary bright spot was absent. These MRI features were more indicative of LHP than of pituitary adenoma. Although the cystic legion is uncommon in LHP, there are some case reports describing this finding.[8 9] The favourable response to treatment with corticosteroid confirmed our diagnosis of LHP.

Lupi *et al* reviewed a total of 44 published cases of LHP and proposed an algorithm for diagnosis and treatment.[10] The proposal recommends that if biopsy cannot be performed, a corticosteroid trial should be started when there is a high clinical index of suspicion of LHP. They also suggested that if the patient does not respond to corticosteroid therapy, a trial with an immunosuppressant agent such as azathioprine should be considered before considering pituitary surgery. Generally, we agree with this proposal and, as discussed below, applied MMF in the management of our patient.

MMF has been used in patients with a variety of autoimmune diseases as well as in cases of renal transplantation. MMF is a prodrug of mycophenolic acid which is an inhibitor of lymphocyte inosine monophosphate dehydrogenase, which acts by drastically decreasing the proliferation of lymphocytes in vitro and in vivo.[6] Although the cause of LHP is unknown, it is histologically characterised by lymphocytic infiltration of the pituitary gland.[10 11] Therefore, MMF is anticipated to be effective for this disease. A literature search of the PubMed database identified one documented case in which MMF was successfully used for the treatment of LHP.[12] Our patient also responded well to MMF with prednisolone. Over the course of a year, prednisolone was successfully tapered to a low dose of 8 mg/day without relapse.

Azathioprine could be another treatment option in our case since its efficacy has been described previously.[10] However, MMF seems to have largely replaced azathioprine in recently established immunosuppressive regimens after kidney transplantation. A systematic review of 23 trials involving 3301 renal transplant recipients showed that MMF is superior to azathioprine in terms of improved graft survival.[5] The report also states that gastrointestinal symptoms are more common adverse events with MMF, whereas thrombocytopaenia and elevated liver enzymes are more common with azathioprine.[5]

As far as we know, there is no head-to-head study that compares the efficacy and tolerability of MMF with azathioprine in the treatment of autoimmune disease. However, azathioprine is often poorly tolerated due to adverse effects, especially in East-Asian populations. For instance, a retrospective study of Japanese patients with ulcerative colitis demonstrated that 33% of the patients were intolerant of azathioprine, experiencing adverse effects such as leukocytopaenia and hepatotoxicity.[13] Also, azathioprine treatment is reported to be difficult to continue in approximately 50% of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis because of similar adverse events.[14] This may be explained in part by genetic polymorphism. Recently, a single-nucleotide polymorphism in the *NUDT15* gene was found to be have strong association with thiopurine-induced leukopaenia, and the variant is more common in East-Asian populations.[15]

LHP is a rare disease, and a standard treatment protocol has not yet been defined for this disease. We present here a case of LHP in which MMF was well tolerated and effective as a second-line agent. Further accumulation of cases is necessary to establish the appropriate treatment regimen for this disease.

Learning points

- Lymphocytic hypophysitis (LHP) is a relatively rare disease characterised by lymphocytic infiltration of the pituitary gland, resulting in pituitary dysfunction.
- LHP is responsive to corticosteroid therapy in most cases, but some cases of recurrence require clinicians to select second-line therapy.
- A definitive diagnosis of LHP can be made only by pathological examination; however, a trial of corticosteroids should be started for suspected cases of LHP even if biopsy cannot be performed.
- Mycophenolate mofetil can be a treatment option in cases of recurrent LHP.

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