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LETTER TO THE EDITOR

Tertiary adrenal insufficiency in a patient with familial Mediterranean fever: Association or coincidence?

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A 16-year-old boy was referred to our hospital due to recurrent fever with chest and abdominal pain. The patient had developed monthly febrile attacks lasting a few days beginning at 10 years of age, but these attacks increased in frequency to twice a month three years later. Familial Mediterranean fever (FMF) was diagnosed based on the clinical symptoms and identification of the MEFV genotype carrying a pathogenic mutation in exon 10 (M694I) and a nonconfirmatory mutation in exon 2 (E148Q). Although oral colchicine 1 mg/day decreased the severity of fever, chest pain, and abdominal pain and improved levels of acute-phase proteins, recurrent febrile attacks persisted, and the patient presented with nonepisodic headache and malaise (Figure 1). Colchicine 1.5 mg/day suppressed the elevated levels of C-reactive protein and serum amyloid A, but headache and malaise did not improve. Considering the previous reports describing the case of hypoadrenal syndrome with FMF, hypoadrenocorticism was suspected due to nonepisodic symptoms.[1,2] While loss of appetite, nausea, arthralgia, weight loss, hyperpigmentation, loss of axillary or pubic hair, or hypotension are often observed with hypoadrenocorticism, the patient showed none of these symptoms. The patient also had no history of prior glucocorticoid use. The early morning cortisol value was 10.2 μg/dL, and the adrenocorticotrophic hormone (ACTH) concentration was 23.3 pg/mL. No abnormalities of electrolytes or leukocyte fractions were identified. Pituitary contrast-enhanced magnetic resonance imaging showed no adenoma, enlargement, or stroke involving the pituitary gland. Contrast-enhanced computed tomography showed no morphological abnormalities or tumors in the adrenal glands. Standard ACTH stimulation tests (250 μg of tetracosactide, injected intravenously) showed a peak serum cortisol concentration of 14 μg/dL (reference, ≥18 μg/dL) at 60 min after injection, indicating adrenal insufficiency. Corticotropin-releasing hormone stimulation tests revealed an ACTH concentration of 12.2 pg/mL before injection and a peak concentration of 63.8 pg/mL (reference, >2-fold increase after stimulation) at 30 min after injection, indicating a normal ACTH response. Insulin tolerance tests (0.1 unit/kg of regular insulin, injected intravenously) indicated lower cortisol and ACTH responses, with a peak serum cortisol concentration of 14 μg/dL (reference, 18-22 μg/dL) and a peak ACTH concentration of 46 pg/mL (reference, ≥150 pg/mL) at 60 min after injection. Nadir serum glucose was 50 mg/dL. Prolonged ACTH stimulation tests showed a ≥3-fold increase in urinary free cortisol. Taken together, the patient was clinically diagnosed with tertiary adrenal insufficiency (TAI) and administration of hydrocortisone at 10 mg/day resulted in slight improvements in

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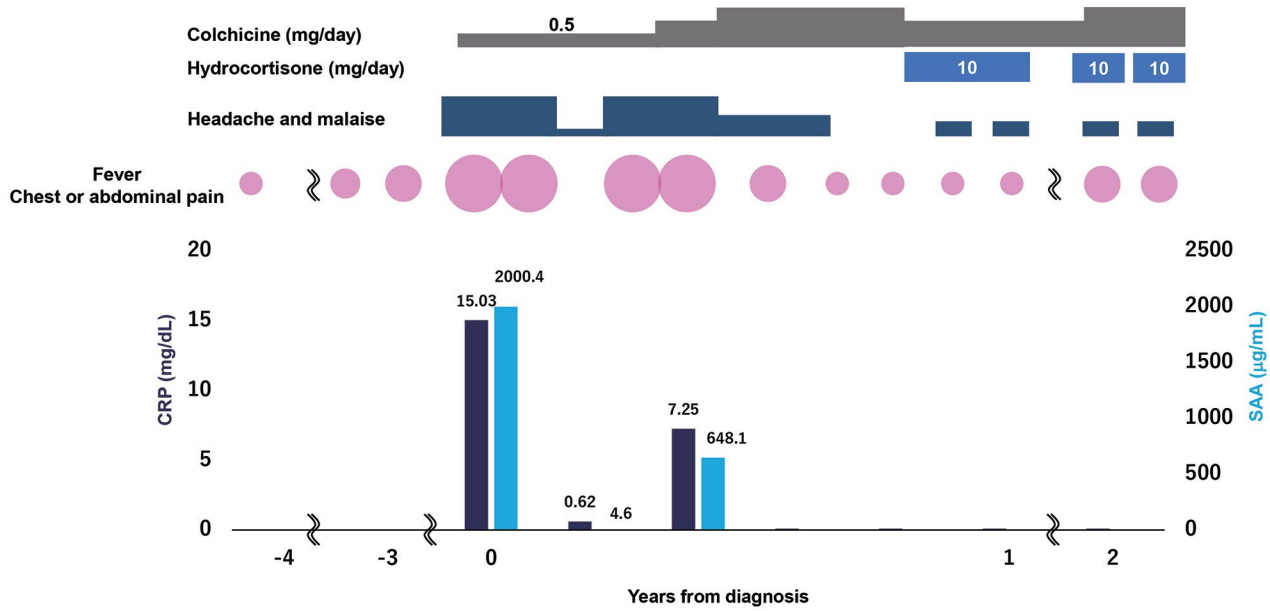

Figure 1. The clinical course of the patient.

headache and malaise. Recurrent fever with episodic headaches has persisted, and thus administration of canakinumab is being planned to suppress recurrent attacks of FMF.

Tertiary adrenal insufficiency is mainly caused by the administration of long-term, supraphysiological doses of glucocorticoids.[3] To the best of our knowledge, this represents the first report of a patient with FMF accompanied by TAI. Familial Mediterranean fever and adrenal insufficiency may present similar symptoms, such as fever, malaise, or arthralgia; therefore, the differentiation of adrenal insufficiency from FMF is challenging due to the heterogeneity of the clinical manifestations of FMF.[1,2] Moreover, in the case of a patient with isolated adrenocorticotropic hormone deficiency, blurring and exacerbating the symptoms of FMF were reported.[4] Therefore, coexistence of adrenal insufficiency should be considered in a patient with FMF, and it is reported that the combination of unexplained shock, nausea, and noninflammatory diarrhea may be suggestive of adrenal insufficiency.[2,4]

Some studies have investigated the function of the hypothalamic-pituitary-adrenal axis in patients with FMF. Serum peak cortisol levels measured with the ACTH stimulation test are higher in the ictal period of patients than in the remission period.[5] In the acute phase of inflammation, increased levels of interleukin (IL)-1 and IL-6 activate the hypothalamus and promote cortisol secretion, inhibiting the production and secretion of inflammatory cytokines, downregulating nuclear factor kappa B and inhibiting inflammation.[4,6] On the other hand, a previous study reported that median levels of serum ACTH in the morning were lower during attacks of FMF than in the healthy control group.[7] Moreover, a lower cortisol response to insulin-induced hypoglycemia suggests that the early cortisol response to hypoglycemic stimulation was deficient, potentially indicating dysfunction of the hypothalamic-pituitary-adrenal axis in FMF patients.[8] Our patient showed blunted cortisol and ACTH responses to insulin tolerance tests, which may suggest an association between FMF and TAI. The efficacy of glucocorticoids in the treatment of FMF remains controversial. Although administration of hydrocortisone in our patient proved insufficient, inadequate cortisol response during febrile attacks may contribute to colchicine resistance in FMF treatment.

In conclusion, the ability to differentiate between adrenal insufficiency and FMF is crucial since both symptoms are similar. It is important to recognize that both diseases can mimic each other, and these pathologies may coexist. Further

studies investigating endocrine function in FMF patients are needed.

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