Necessity of Utilizing Physiological Glucocorticoids for Managing Familial Mediterranean Fever

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Patient: Male, 35-year-old
Final Diagnosis: Familial Mediterranean fever
Symptoms: Chest pain • fever
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course
Background: Familial Mediterranean fever is an auto-inflammatory disease caused by pyrin mutations. Glucocorticoids inhibit the production and secretion of inflammatory cytokines, including IL-6 and IL-1β, from inflammatory cells and suppress the activation of nuclear factor-kB in the nucleus. However, the functions of physiological glucocorticoids in the disease remain unknown.

Case Report: We report the case of a Japanese man with familial Mediterranean fever complicated by isolated adrenocorticotropic hormone deficiency. Patient non-compliance with hydrocortisone replacement therapy led to a series of pericarditis and fever episodes. Subsequently, the regular administration of colchicine alone could not prevent auto-inflammation. The clinical course of treatment suggested that the absence of physiological levels of glucocorticoids is crucial for familial Mediterranean fever attacks. Because familial Mediterranean fever is a pyrin abnormality-induced auto-inflammatory disease that subsequently activates cytokines via the nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing 3 inflammasomes and the absence of glucocorticoids can exacerbate the severity of the auto-inflammatory disease.

Conclusions: Physiological glucocorticoid levels appear to be essential for the regulation of inflammasome activation via IL-6-negative regulation. However, pharmacological levels of glucocorticoids are not currently used for the prevention of familial Mediterranean fever attacks. Physicians should be aware of adrenal insufficiency as a possible disorder when they encounter cases of refractory familial Mediterranean fever.

MeSH Keywords: Adrenal Insufficiency • Colchicine • Familial Mediterranean Fever • Glucocorticoids

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Background

Familial Mediterranean fever (FMF) is an auto-inflammatory disease caused by FMF gene (MEFV) mutations [1] that lead to interleukin-1β activation. Colchicine ameliorates FMF through microtubule polymerization and is reportedly effective for over 90% of patients [2]. Interleukin (IL)-1, IL-6, and tumor necrosis factor are all elevated in FMF and are considered to be targets for add-on biologics to colchicine treatments, especially in patients with colchicine-resistant or intolerant FMF [3].

Isolated adrenocorticotropic hormone (ACTH) deficiency is categorized as a central adrenal insufficiency, and is caused by various factors, including external glucocorticoid use [4]. Physiological levels of glucocorticoids are required for daily life. In addition, pharmacological levels of glucocorticoids are required to avoid adrenal crisis when sick, the same as with primary adrenal insufficiency [5].

In the present case, insufficient hypothalamus-pituitary-adrenal (HPA) axis function was found to result in a series of attacks when prompt supplementation with GC was not administered [6]. Although the role of GC in FMF inflammation remains unclear, this case suggests the importance of a physiological dose of GC as a self-limiting factor.

Case Report

A 35-year-old Japanese man was referred to our hospital with subacute onset of chest pains and fever. He had isolated adrenocorticotropic hormone (ACTH) deficiency and had been treated with 15 mg/d of hydrocortisone since he was 24-years-old, although his medication was intermittently taken for several months before admission. He was a non-smoker, non-alcohol consumer, and did not use illegal drugs. Both his white blood cell (WBC) count and C-reactive protein (CRP) levels were elevated (Table 1), and ultrasonography and computed tomography (CT) scans revealed pericardial effusion with thickened pleura and pericardium (Figure 1). There was no evidence of viral infection or auto-inflammatory disease, and he was diagnosed with idiopathic pericarditis. Adrenal insufficiency was noted upon laboratory analysis at admission in December 2013, and he was thus treated with 100 mg/d of hydrocortisone infusion (Figure 2).

His pericarditis recurred twice within 1 year after discharge. Recurrent serositis and fever with no specific cause led us to suspect FMF. DNA analysis revealed compound heterozygous mutations in exons 1 and 2 of the MEFV gene, which encodes pyrin (E84K and E184Q). These mutations were previously reported in cases of FMF in Japan [7]. Based on the clinical manifestations and DNA analysis, he was diagnosed with FMF [8] and treated with 2 mg/d of colchicine. Thereafter, he was free from FMF attacks for 20 months. However, his non-compliance

Table 1. Patient assessment results on admission in December 2013.

| Variables                      | Values | Reference range  | Variables                  | Values | Reference range |
|--------------------------------|--------|------------------|-----------------------------|--------|-----------------|
| Complete cell count            | WBC, /μL | 8700            | T. Bil, mg/dL               | 0.9    | 0.2–1.2        |
| Neutrophil, %                  |        | 63.4            | AST, IU/L                   | 48     | 8–38           |
| Lymphocyte, %                  |        | 30.2            | ALT, IU/L                   | 21     | 4–44           |
| Monocyte, %                    |        | 3.1             | LDH, IU/L                   | 162    | 119–229        |
| Eosinophil, %                  |        | 2.3             | ALP, IU/L                   | 177    | 104–338        |
| Hemoglobin, g/dL               |        | 12.0            | CK, IU/L                    | 51     | 60–287         |
| Platelet, ×10^3/μL             |        | 70              | Na, mmol/L                  | 129    | 135–147        |
| Serum chemistry                |        |                 | K, mmol/L                   | 4.0    | 3.3–4.8        |
| Total protein, g/dL            |        | 5.7             | Cl, mmol/L                  | 97     | 98–106         |
| Albumin, g/dL                  |        | 3.3             | CRP, mg/dL                  | 8.08   | <0.3           |
| BUN, mg/dL                     |        | 20              | BNP, pg/mL                  | 132.2  | <18.4          |
| Cre, mg/dL                     |        | 0.8             | Log10 BUN                   | 2.0     | 0.7–2.4         |
| Uric acid, mg/dL               |        | 1.02            | Log10 Cre                   | 0.3     | 0.5–0.8         |

AST – aspartate aminotransferase; ALP – alkaline phosphatase; ALT – alanine aminotransferase; BNP – brain natriuretic peptide; BUN – blood urea nitrogen; CK – creatinine kinase; Cre – creatinine; CRP – C-reactive protein; LDH – lactate dehydrogenase; T. Bil – total bilirubin; WBC – white blood cell.
with hydrocortisone replacement therapy, while continuing colchicine therapy, led to the recurrence of FMF (Figure 2).

Laboratory data from the latest admission (March 2016) are shown in Table 2. The percentage of neutrophil was elevated, with high-normal WBC counts. In addition, CRP and IL-6 levels were elevated, but the IL-1β levels were normal. CT imaging revealed pericardial effusion and thickened pleura and pericardium. Thus, intravenous infusions of 100 mg/d of hydrocortisone (for 2 days in the acute phase, followed by a gradual reduction) were provided, and 2 mg/d of colchicine was orally administered, but non-steroidal anti-inflammatory drugs were retained. Acute pericarditis was relieved within a few days, and the patient was encouraged to continue GC replacement therapy (Figure 2).

### Discussion

This is the first reported case of FMF with adrenal insufficiency, suggesting that FMF-related inflammation can be exacerbated due to adrenal insufficiency and is ameliorated by glucocorticoid administration. Furthermore, it suggests that physiological GC may be essential for regulating inflammasome activation via IL-6 suppression.

Colchicine ameliorates FMF attack in most patients [2]; however, in the present case, FMF attack recurred when hydrocortisone was neglected, even when colchicine was taken regularly. Prompt GC administration is reportedly effective in regulating the early stage of acute serositis in FMF [9], although GC potentially triggers the nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing 3 (NLRP3) inflammasome cascade [10]. GC may regulate the early phase of colchicine-independent inflammation by reducing the expression of nuclear factor-κB (NF-κB), which activates inflammatory agents such as IL-6. A physiological dose of GC may be necessary to prevent the dysregulation of organelle network-related auto-inflammatory responses and is possibly associated with the prevention of FMF attacks (Figure 3).

FMF is an auto-inflammatory disease caused by mutations in pyrin [11], an inflammasome adaptor in NLRP3. Oligomerization of apoptosis-associated speck-like proteins containing a caspase-recruitment domain (ASC) leads to formation of the NLRP3 inflammasome and activates caspase-1 and several inflammatory cytokines such as IL-1β. During the acute phase of inflammation, increased IL-6 activates the HPA axis and increases cortisol secretion as a self-limiting factor. GC inhibits the production and release of inflammatory cytokines such as

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### Table 2. Patient inflammation markers on admission in March 2016.

| Variables                      | Values | Reference range |
|--------------------------------|--------|-----------------|
| WBC, /μL                       | 7240   | 3300–9000       |
| Neutrophil, %                  | 72     | 40–69           |
| C-reactive protein, mg/dL      | 3.41   | ≤0.3            |
| Interleukin-1β, pg/mL          | <10    | <10             |
| Interleukin-6, pg/mL           | 456    | 4.0             |

WBC – white blood cell.

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**Figure 1.** Computed tomographic imaging. White arrows indicate the thickened pleura with pericardial effusion.

**Figure 2.** Clinical treatment course in this case study of familial Mediterranean fever. Intermittent hydrocortisone replacement led to adrenal insufficiency and repeated exacerbation of the familial Mediterranean fever symptoms. Administration of hydrocortisone rapidly relieved both the fever and the chest pain. HC – hydrocortisone; CRP – C-reactive protein; NSAIDs – non-steroidal anti-inflammatory drugs.
IL-1β, IL-6, and tumor necrosis factor-α, and downregulates NF-κB [12], thus activating NLRP3, pro-IL-1β, and pro-IL-18. Impairment of the physiological response to GC can exacerbate the severity of auto-inflammatory diseases. An early blunted response to an insulin stimulation test involving FMF patients, relative to healthy controls, was previously reported [13]. Similar impairments of the HPA response have been demonstrated in other autoimmune diseases such as rheumatoid arthritis and Sjögren’s syndrome [14,15]. In the present case, defects in the HPA axis deferred the response to IL-6 and presumably led to the exacerbation of inflammation. Because the FMF attack recurred in parallel with his adrenal insufficiency, GC may be required to prevent the FMF attacks. In particular, because IL-1β levels were low after colchicine administration, physiological GC possibly prevented the FMF attack in an IL-1β-independent manner.

**Conclusions**

Treatment of GC insufficiency was crucial to sustain the attack-free period of FMF in the present case, potentially providing novel insights into the under-appreciated role of physiological GC levels in auto-inflammatory diseases. Therefore, adrenal insufficiency, including relative insufficiency, should be considered when the physician is confronted with both controlled and uncontrolled FMF cases. However, further case series or clinical studies are required to confirm the relationship between adrenal insufficiency and FMF attack.

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**Department and institution where work was done**

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**Conflicts of interest**

None.
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