A Case of Hemophagocytic Lymphohistiocytosis following Second Dose of COVID-19 Vaccination

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Keywords
Hemophagocytic lymphohistiocytosis · COVID-19 · Pandemic · SARS-CoV-2 vaccine

Abstract
Hemophagocytic lymphohistiocytosis (HLH) is a rare, severe hyperinflammatory disease characterized by overproduction of cytokines and hemophagocytosis of hematopoietic cells, resulting in multiorgan failure. Prompt treatment initiation is essential for patient survival. The coronavirus disease 2019 (COVID-19) pandemic has led to the rapid development of several vaccines, including BNT162b2 by Pfizer-BioNTech. Few cases of immune-mediated complications of COVID-19 and its vaccines have been reported, characterized by persistent stimulation of the immune system, resembling HLH. We report the case of a 21-year-old man with secondary HLH following a second dose of the BNT162b2 vaccine. The patient did not have primary HLH or other contributors to secondary HLH and met the HLH-2004 diagnostic criteria. He was safely treated with steroid pulse therapy alone, without etoposide, cyclosporin, or immunoglobulins, which are recommended for pediatric patients. Physicians need to be aware of such severe complications following a second dose of the COVID-19 vaccine.

Introduction
The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to the rapid production of several vaccines [1]. Currently, there are two messenger RNA (mRNA)-based vaccines (BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna Therapeutics) and two DNA vaccines utilizing adenovirus vectors (ChAdOx1 nCov-19 by AstraZeneca-Oxford and Ad26.COV2.S by Janssen-Johnson & Johnson). Although there was a significant decrease in COVID-19-associated mortality, various adverse events have been described after vaccination [2]. Most were in the form of mild localized or systemic symptoms such as injection site pain, fever, myalgia, headache, or fatigue which subsided spontaneously with conservative care only [3]. However, rare but fatal adverse events, including thrombotic thrombocytopenia and myocarditis, were also reported, and as the number of vaccinated people increased, its frequency increased [4, 5]. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening, hyperferritinemic, hyperinflammatory syndrome, and HLH as a complication of COVID-19 vaccination has rarely been reported, regardless of vaccine type; all but one case occurred at the first dose [6–14]. Herein, we report a case of HLH following the second dose of BNT162b2 vaccination.
Case Report

A 21-year-old man was transferred from another hospital with an uncontrolled high fever (above 39°C), profound pancytopenia, and an elevated total bilirubin concentration (10.27 mg/dL). He experienced general weakness, a fever, myalgia, and a skin rash without an itching sensation. The patient had no known or related medical history and was in good physical condition before receiving the second dose of the BNT162b2 vaccine 2 weeks ago. He was started on empirical intravenous antibiotics (Tazoperan™, piperacillin and tazobactam, 4.5 g, q8h) for fever of unknown origin and steroid pulse therapy (intravenous methylprednisolone, 1.5 mg/kg/day) 4 days before the transfer.

Table 1. Diagnostic criteria of HLH and laboratory results of a 21-year-old man

| Diagnostic criteriaa | At diagnosis | Day 26 |
|----------------------|--------------|--------|
| Molecular diagnosis consistent with HLH | Not evaluated | – |
| Diagnostic criteria for HLH fulfilled (≥5 of 8 criteria) | 8 of 8 | – |
| Fever | 39.5°C | 36.4°C |
| Splenomegaly | Yes | – |
| Cytopenias (affecting ≥2 of 3 lineages) | 2 lineages | – |
| Hemoglobin <90 g/dL | 9.6 | 13.6 |
| Platelets <100 × 10⁹/L | 37 | 205 |
| Neutrophils <1.00 × 10⁹/L | 0.35 | 4.20 |
| Fasting hypertriglyceridemia and/or hypofibrinogenemia | – |
| Fasting triglycerides ≥3.0 mmol/L | 32.4 | 4.4 |
| Fibrinogen ≤1.5 g/L | 1.3 | 1.62 |
| Hemophagocytosis in BM | Yes | – |
| Low or no NK cell activity | Yes | – |
| Ferritin ≥500 μg/L | 23,639 | 204 |
| Soluble CD25 ≥2,400 U/mL | 5,776 | – |
| Other laboratory results (reference range) | – |
| Aspartate aminotransferase (normal range, 0–40), U/L | 292 | 24 |
| Alanine aminotransferase (normal range, 0–40), U/L | 359 | 45 |
| Total bilirubin (normal range, 0–1.20), mg/dL | 10.27 | 1.12 |
| Direct bilirubin (normal range, 0.13–0.47), mg/dL | 9.59 | 0.91 |
| Lactate dehydrogenase (normal range, 0–250), U/L | 881 | 217 |
| Albumin (normal range, 3.5–5.2), g/dL | 3.0 | 4.8 |
| Urea nitrogen (normal range, 6.0–20.0), mg/dL | 19.4 | 17.6 |
| Creatinine (normal range, 0.70–1.20), mg/dL | 0.80 | 0.81 |
| C-reactive protein (normal range, 0–0.5), mg/dL | 1.3 | <0.03 |

HLH, hemophagocytic lymphohistiocytosis. aHLH-2004 diagnostic criteria.

Fig. 1. a PET-CT reveals intense FDG uptake in the bone marrow, and an increased uptake, but to a lesser extent, in the liver. The spleen did not exhibit FDG uptake. PET-CT can be a valuable tool to exclude secondary causes of HLH and identify sites of hemophagocytosis. b Bone marrow aspirates demonstrating evidence of hemophagocytosis (×400).
Physical examination revealed an erythematous rash on the patient’s arms and upper chest, icteric conjunctivae, and splenomegaly. No clinical features of thrombosis were observed. Computed tomography (CT) of the patient’s neck, chest, and abdomen/pelvis demonstrated hepatosplenoemegaly (spleen size, 13 cm) with periportal edema and gallbladder wall thickening, minimal pelvic ascites and bilateral pleural effusion, and no focus of infection. Blood and urine cultures were negative. Upon 18F-fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET)-CT, liver uptake was relatively even (standardized uptake value max/mean, 3.2/2.3), and FDG activity was not increased in the spleen (shown in Fig. 1a). A bone marrow biopsy revealed normocellular marrow with substantial histiocytosis and active hemophagocytosis, without any malignant cell infiltration (shown in Fig. 1b). A real-time polymerase chain reaction of oro- and nasopharyngeal swabs was negative for SARS-CoV-2 and other respiratory viruses. Furthermore, there was no evidence of acute or active infection with cytomegalovirus; Epstein-Barr virus; parvovirus B19; hepatitis A, B, and C; human immunodeficiency virus (HIV); or Korean endemic viruses related to hemorrhagic fever with renal syndrome. Autoimmune antibody tests, conducted to rule out the possibility of an underlying autoimmune disease, were also negative.

Overall, the patient’s test results met the HLH-2004 diagnostic criteria, with an HScore of 319 (>99% probability of hemophagocytic syndrome) [15–17]. The laboratory results of the patient at presentation and the results of infection and autoimmune disorder profiles are presented in Tables 1 and 2. The patient subsequently received high-dose dexamethasone (20 mg/day for 7 days) and a 25% dose reduction on a weekly basis without etoposide or other treatment modalities. Nineteen days after steroid pulse therapy, the patient was discharged in good physical condition without any evidence of HLH relapse.

### Discussion

HLH is a rare disorder characterized by an overwhelming systemic inflammatory reaction. The aberrant activation of macrophages, natural killer cells, and cytotoxic T cells leads to the overproduction of cytokines, especially interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor-alpha, as well as hemophagocytosis of hematopoietic cells in the bone marrow. The resulting tissue/organ destruction means that the disease is life-threatening. Multisystem inflammatory syndrome in children (MIS-C), also a disorder caused by the dysregulated immune system, is associated with SARS-CoV-2 infection [18]. MIS-C is similar to HLH in increased T-cell activation and plasma cytokines/chemokines, but differs in the extent of the stimulation. Patients with MIS-C usually present with cardiac problems including myocarditis and often involve gastrointestinal disorders. Patients with HLH experience an unremitting high fever, cytopenia, coagulopathy, hepatic dysfunction, and organomegaly, with or without lymphadenopathies. If not treated appropriately, the patient’s condition may rapidly deteriorate to terminal multiorgan failure and subsequent death [16]. Therefore, early diagnosis and urgent treatment are critical for survival [15]. HLH can be classified as either familial,

| Diagnostic markers | Result |
|--------------------|--------|
| SARS-CoV-2 RNA | Negative |
| Parvovirus B19 PCR | Negative |
| HIV antibody | Negative |
| Hepatitis A antibody IgM | Negative |
| HBV profile | |
| HBV surface antigen | Negative |
| HBV surface antibody | 365.92 IU/L |
| HBV core antibody IgG | Positive |
| HBV core antibody IgM | Negative |
| HBV DNA PCR (copies/mL) | <116 |
| Hepatitis C virus antibody | Negative |
| Plasma CMV DNA RT-qPCR (copies/mL) | <500 |
| Plasma EBV DNA RT-qPCR (copies/mL) | <500 |
| EBV early antibody IgG | Negative |
| EBV nuclear antibody IgG | Positive |
| EBV capsid antibody IgG | Positive |
| EBV early antibody IgM | Negative |
| EBV capsid antibody IgM | Negative |
| Hantaan virus antibody | Negative |
| Leptospira antibody | Negative |
| Orientia tsutsugamushi antibody | Negative |
| Autoimmune antibodies | |
| Anti-nuclear antibody | Negative |
| Anti-dsDNA antibody | Negative |
| Anti-Smith antibody | Negative |
| Rheumatoid factor | Negative |
| Anti-neutrophil cytoplasmic antibody | Negative |
| C3/C4 | Normal/normal |
| CH50 | Normal |
| Lymphocyte subset | |
| T (CD3) % (normal range, 61–85) | 91.3 |
| T4 (CD4) % (normal range, 28–58) | 16.6 |
| T8 (CD8) % (normal range, 19–48) | 74.8 |
| B (CD19) % (normal range, 7–23) | 4.6 |
| NK (CD3-CD56+CD16+) % (normal range, 61–85) | 3.7 |
| NKT (CD3+CD56+) % | 0.7 |

CMV, cytomegalovirus; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; HBV, hepatitis B virus; NK, natural killer; NKT, natural killer T; RT-qPCR, reverse transcriptase quantitative polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
## Table 3. Clinical characteristics and treatment outcomes of patients with HLH after SARS-CoV-2 vaccination

| No. | Case 1 [8] | Case 2 [7] | Case 3 [8] | Case 4 [9] | Case 5 [9] | Case 6 [10] | Case 7 [10] | Case 8 [10] | Case 9 [11] |
|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Age/sex | 68/M | 43/F | 36/F | 20/M | 71/F | 60s/M | 70s/F | 30s/M | 85/M |
| Underlying | Hypertension | Gout | Bowen’s disease | EBV 824 copies/mL in plasma | None | None | Hypertension | Type 2 DM | ET | Breast cancer in remission | Ankylosing spondylitis | None |
| Vaccine | ChAdOx1 nCov-19 | Inactivated SARS-CoV-2 | ChAdOx1 nCov-19 | BNT162b2 | ChAdOx1 nCov-19 | ChAdOx1 nCov-19 | ChAdOx1 nCov-19 | ChAdOx1 nCov-19 | BNT162b2 |
| Symptom onset | 10 days after 1st vaccination | Shortly after 1st vaccination | 9 days after 1st vaccination | 2 days after 1st vaccination | 7 days after 1st vaccination | 5 days after 1st vaccination | 7 days after 1st vaccination | 8 days after 1st vaccination | Shortly after 1st vaccination |
| Organomegaly | Splenomegaly and LAPs | No | Hepatosplenomegaly and LAPs | Splenomegaly and LAPs | Hepatomegaly | No | Splenomegaly | No |
| Neutrophils, 10^9/L | N/A | 0.70 | 31.20 | 0.72 | 0.32 | N/A | N/A | N/A | 9.2 |
| Hemoglobin, g/dL | N/A | 11.3 | 11.5 | 13.2 | 14.6 | 10.1 | 11.9 | 10.5 | Normal |
| Platelets, 10^9/L | 59 | 27 | 243 | 86 | 26 | 54 | 69 | 319 | 34 |
| Ferritin, μg/L | 11,801 | 8,140 | 12,423 | 6,592 | >16,500 | 159,076 | 5,529 | 58,255 | 378 |
| Triglycerides | 2.3 mmol/L | 2.4 mmol/L | 1.8 mmol/L | 5.9 mmol/L | 27.8 mmol/L | 6.3 mmol/L | 2.0 mmol/L | 2.7 mmol/L | 2.7 mmol/L |
| Fibrinogen | 2.3 g/L | 1.4 g/L | 5.5 g/L | 9.9 g/L | 9.3 g/L | 0.7 g/L | 0.9 g/L | 4.2 g/L | 4.3 g/L |
| BM hemophagocytosis | Yes | Yes | N/A | Yes | Yes | Yes | Yes | Yes | Yes |
| Soluble CD25 | 733 U/mL | 204.99 pg/mL | N/A | 2,806 U/mL | 2,703 U/mL | 4,833 pg/mL | 9,232 pg/mL | 3,575 pg/mL | N/A |
| NK cell activity | Normal | Decreased | N/A | Decreased | Normal | N/A | N/A | N/A | N/A |
| HScore | 250 | 261 | N/A | 229 | 293 | 259 | 220 | 219 | N/A |
| Other complications | No | No | No | No | No | DVT | Bilateral pleural effusions Multiorgan failure | Acute pneumonitis | LV dysfunction |
| Treatment | Not treated | Dexamethasone | Methylprednisolone + IVG | Dexamethasone | Dexamethasone + etoposide | Methylprednisolone + IVG + anakinra | Methylprednisolone + IVG + anakinra | Methylprednisolone + IVG + anakinra | N/A |
| Outcomes | Alive | Alive | Alive | Alive | Alive | Alive | Alive | Died⁹ | Alive |

⁹ Died due to multiorgan failure.
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| No. | Case 10 [12] | Case 11 [12] | Case 12 [12] | Case 13 [12] | Case 14 [12] | Case 15 [13] | Case 16 [14] | Case 17 (our case) |
|-----|--------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------------|
| Age/sex | 52/M | 53/M | 57/M | 55/F | 48/F | 38/F | 24/F | 21/M |
| Underlying | T-cell lymphoma | ILD | Controlled HIV | MDS, MAC, aspergillosis | HIV/AIDS | MAC-IRIS | None | None | None |
| Vaccine | BNT162b2 | BNT162b2 | mRNA-1273 | BNT162b2 | mRNA-1273 | BNT162b2 | BNT162b2 | BNT162b2 |
| Symptom onset | 1 day after 1st vaccination | 4 days after 1st vaccination | 12 days after 1st vaccination | 8 days after 1st vaccination | 21 days after 2nd vaccination | 10 days after 1st vaccination | 14 days after 2nd vaccination |
| Organomegaly | Splenomegaly | Hepatomegaly | No | Hepatosplenomegaly | No | N/A | Splenomegaly | Splenomegaly |
| Neutrophils, 10^9/L | WBC count, 5.4 | WBC count, 3.0 | WBC count, 4.7 | WBC count, 2.6 | WBC count, 10.6 | 0.9 | WBC count, 1.95 | 0.35 |
| Hemoglobin, g/dL | 11.1 | 11.5 | 8.4 | 6.8 | 12.1 | 9.8 | Anemia | 9.6 |
| Platelets, 10^9/L | 172 | 21 | 9 | 106 | 310 | N/A | Thrombocytosis | 37 |
| Ferritin, μg/L | 8,130 | 75,249 | >15,000 | 7,724 | 285 | 500 | 138 | 23,639 |
| Triglycerides | 650 mg/dL | 263 mg/dL | 142 mg/dL | 106 mg/dL | 138 mg/dL | 225 mg/dL | Elevated | 32.4 mmol/L |
| Fibrinogen | 105 mg/dL | 435 mg/dL | <35 mg/dL | 561 mg/dL | 527 mg/dL | normal | Elevated | 1.3 g/L |
| BM hemophagocytosis | Yes | Yes | N/A | N/A | N/A | Yes | No | Yes |
| Soluble CD25 | 25,603 pg/mL | 18,100 pg/mL | 2,473 pg/mL | 4,907 pg/mL | N/A | 2,610 U/mL | N/A | 5,776 U/mL |
| NK cell activity | N/A | N/A | N/A | N/A | N/A | Decreased | N/A | Decreased |
| HScore | 239 | 213 | 185 | 208 | 130 | 147 | 259 | 319 |
| Other complications | Bacteroides bacteremia | ILD aggravation | Respiratory failure | No | Relapsing pulmonary IRIS flares | No | No | Skin rash |
| Treatment | Dexamethasone + etoposide | Dexamethasone + IVG + anakinra | Methyprednisolone + anakinra | Prednisone + infliximab | Methyprednisolone | Dexamethasone + IVG + anakinra | Methyprednisolone | Dexamethasone |
| Outcomes | Died | Alive | Died | Alive | Alive | Alive | Alive | Alive |

BM, bone marrow; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; DVT, deep vein thrombosis; EBV, Epstein-Barr virus; ET, essential thrombocythemia; HIV, human immunodeficiency virus; ILD, interstitial lung disease; IRIS, immune reconstitution inflammatory syndrome; IVG, intravenous immunoglobulin; LAPs, lymphadenopathies; LV, left ventricle; MAC, Mycobacterium avium complex; MDS, myelodysplastic syndrome; mRNA, messenger RNA; NK, natural killer; PTE, pulmonary thromboembolism; WBC, white blood cell; SARS-COV-2, severe acute respiratory syndrome coronavirus 2. a All patients had negative COVID-19 serology test results. The patient’s EBV serology profile (EB-VCA IgA negative, EB-VCA IgM negative, EB-VCA IgG positive, EB-VEA IgA negative, EB-VEA IgG negative, and EB-VNA IgG positive) showed that the EBV infection was not a recent event. b All patients with LAPs underwent lymph node biopsy to exclude malignancy. c The reports used different units and reference ranges of soluble CD25. The soluble CD25 reference ranges were 27–118 U/mL and 0–2,500 pg/mL. d This patient developed atrial fibrillation with hemodynamic compromise and spontaneous pneumothorax and was moved to the intensive care unit for vasopressors, continuous veno-venous hemofiltration, and chest drains. However, the patient died because of spontaneous rupture of the esophagus. The reports used different units and reference ranges of soluble CD25. The soluble CD25 reference ranges were 27–118 U/mL and 0–2,500 pg/mL.
characterized by genetic defects causing lymphocyte cytotoxicity (mutations of various genes, such as PRF1, STX11, UNC13D, or STXB2) [19], or acquired/secondary HLH (sHLH), usually triggered by infection, autoimmune disease, or malignancy [20–22]. In particular, it is critical to exclude malignancy-associated HLH due to lymphomas including intravenous B-cell lymphoma and aggressive T-cell lymphoma in Asian populations, considering the high prevalence and similar clinical features [22]. The diagnosis of HLH is commonly based on the criteria of the HLH-2004 study, which were developed using pediatric patient data; it has not been validated in adults [15]. An alternative is the HScore, a diagnostic scoring system for HLH developed based on clinical parameters of the adult population [17]. In this case, the patient met the criteria for both measures: he fulfilled all eight of the HLH-2004 diagnostic criteria and had an HScore of 319. There was no clear precipitant of HLH other than the second dose of the BNT162b2 vaccine. The patient had no remarkable medical history, was not taking any medications, and had no active or recent bacterial or viral infection or autoimmune disease. After his diagnosis, the patient recovered entirely without relapse or sequelae with the administration of dexamethasone steroid pulse therapy with slow tapering; the HLH-94 treatment protocol was not strictly followed [20]. The HLH-94 protocol was initially designed for pediatric patients; it includes administering steroids, etoposide, cyclosporin, and immunoglobulins. The schedule and dosage should be modified for adults to avoid severe complications related to comorbidities or multiorgan damage caused by cytokine storms [16].

sHLH was previously reported in patients who had a SARS-CoV-2 infection. Furthermore, as sHLH is similar to hyperinflammatory syndrome, it may be underdiagnosed in severe cases of COVID-19 [23]. Administration of the IL-1 inhibitor, anakinra, and the IL-6 inhibitor, tocilizumab, showed improvements in patients hospitalized with COVID-19-induced sHLH and severe COVID-19, respectively [24, 25]. Recent studies also suggest that the anti-interferon gamma antibody, emapalumab, and the JAK1/2 inhibitor, ruxolitinib, are available treatment options for sHLH [16, 26, 27]. Although the mechanisms of COVID-19 vaccination-related sHLH remain unknown, overwhelming immune stimulation by mRNA- or DNA-based vaccines may trigger a massive cytokine storm, which may result in sHLH. We are aware of 17 cases of SARS-CoV-2 vaccination-related sHLH to date, including our case (Table 3) [6–14]. All of these cases fulfilled the diagnostic criteria of either HLH-2004 or the HScore after receiving the BNT162b2 (n = 8), ChAdOx1 nCov-19 (n = 6), mRNA-1273 (n = 2), and inactivated SARS-CoV-2 (n = 1) vaccinations. Secondary causes of HLH were excluded by extensive infection screening and autoimmune panels. Most of the patients with COVID-19 vaccination-related sHLH experienced symptomatic onset at a median of 7.0 (range, 0–21) days, and 15 of 17 were after the first dose. Therefore, physicians should be aware that, although rare, sHLH is a potentially catastrophic complication of any currently available COVID-19 vaccine, after either the first or second dose. We suggest that patients be closely monitored for any constitutional symptoms or laboratory abnormalities after vaccination for at least 3 weeks.

In one of the 17 patients, sHLH completely resolved without any treatment (case 1) [6]. For another patient, treatment and clinical outcomes were not reported (case 9) [11]. The other patients received steroid pulse therapy (n = 15), in some cases combined with either etoposide (n = 2) or another second-line therapy, such as anakinra (n = 5) or infliximab (n = 1), and/or immunoglobulin infusion (n = 5); the steroids were gradually tapered, and there was no relapse of sHLH. Although we did not utilize second-line therapy in our case, anakinra reportedly has a tolerable safety profile and acceptable clinical outcomes in patients with sHLH related to COVID-19 infection or vaccination [10, 12, 14, 23]. Therefore, we suggest utilizing corticosteroids as the treatment backbone and adding anakinra in severe cases, in which sHLH cannot be controlled solely with corticosteroids. Three of the patients died, all with substantial comorbidities (case 7, breast cancer and essential thrombocytopenia; case 10, lymphoma; and case 12, HIV infection) [10, 12].

This case report should not be used as support to avoid vaccination, as the vaccine remains an essential and promising tool to overcome the COVID-19 pandemic. We believe that early recognition and initiation of corticosteroids, combined with anakinra in severe cases, are critical to prevent irreversible organ damage and death. Therefore, vaccinated patients should be carefully monitored for signs and symptoms of HLH.

**Statement of Ethics**

This case report was approved by the Institutional Review Board and Ethics Committee of the Catholic Medical Center, Republic of Korea (KC22ZASE0149), and was conducted in accordance with the tenets of the Helsinki Declaration. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.
**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

This research was supported by Catholic University of Korea Open Access Agreements.

**Author Contributions**

Hee Won Park and Gi June Min were the treating physicians and participated in the study design and writing of the manuscript. Tong Yoon Kim and Seok-Goo Cho contributed to the writing of the manuscript and discussion of the case with the literature review. Seok-Goo Cho reviewed the manuscript. Gi June Min participated in the pathological analyses and discussion of the study design. All authors have read and approved the final manuscript.

**Data Availability Statement**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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