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CASE REPORT

Hemophagocytic lymphohistiocytosis triggered by relapsing polychondritis: A case report

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Abstract

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disorder caused by abnormal histiocytes and T cell activation. In adults, it is predominantly associated with infections, cancers, and autoimmune diseases. Relapsing polychondritis (RP), another rare disease, is diagnosed based on symptoms without specific tests, featuring cartilage inflammation characterized by swelling, redness, and pain, rarely inducing HLH.

CASE SUMMARY

A 74-year-old woman visited the emergency room with a fever of 38.6 °C. Blood tests, cultures, and imaging were performed to evaluate fever. Results showed increased fluorescent antinuclear antibody levels and mild cytopenia, with no other specific findings. Imaging revealed lymph node enlargement was observed; however, biopsy results were inconclusive. Upon re-evaluation of the physical exam, inflammatory signs suggestive of RP were observed in the ears and nose, prompting a tissue biopsy for confirmation. Simultaneously, persistent fever accompanied by cytopenia prompted a bone marrow examination, revealing hemophagocytic cells. After finding no significant results in blood culture, viral markers, and tissue examination of enlarged lymph nodes, HLH was diagnosed by RP. Treatment involved methylprednisolone followed by azathioprine. After two months, bone marrow examination confirmed resolution of hemophagocytosis, with normalization of hyperferritinemia and pancytopenia.

CONCLUSION

Thorough physical examination enabled diagnosis and treatment of HLH trig-

gered by RP in patients presenting with fever of unknown origin.

Key Words: Hemophagocytic lymphohistiocytosis; Relapsing polychondritis; Autoimmune disease; Fever of unknown origin; Steroid; Case report

Core Tip: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition typically triggered in adults by conditions such as cancer, infections, and autoimmune disorders, resulting in immune system over-activation. Relapsing polychondritis (RP), an uncommon disease, is diagnosed through physical examination. In contrast to primary HLH, which necessitates stem cell transplantation is the only definitive cure, acquired HLH can be managed with therapies such as chemotherapy and immunosuppressive therapy, tailored to the underlying cause. The patient received treatment for HLH using RP therapies and was successfully cured with methylprednisolone (1 mg/kg) and azathioprine.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease that results from immune system dysregulation and is characterized by recurrent fever, cytopenia, reactive marrow, and hepatosplenomegaly. It is a response caused by overactivation of the cluster of differentiation (CD) 8 + T cells and antigen-presenting cells, inducing a cytokine storm[1, 2]. Immune regulation leads to elevated levels of interferon-γ, tumor necrosis factor (TNF), and soluble CD8, resulting in fever, increased ferritin, hypertriglyceridemia, and hypofibrinogenemia based on HLH-2004 diagnostic criteria[1]. However, these criteria are based on genetic HLH rather than adult HLH, necessitating a comprehensive evaluation for diagnosis in adults[3]. Diagnostic and therapeutic approaches are challenging because of the need for prior confirmation of potential triggers such as infections, malignancies, and autoimmune conditions[3].

Relapsing polychondritis (RP) is characterized by the invasion of cartilaginous structures (ear, nose, larynx, tracheobronchial tree, and ribs) and other connective tissue organs. Although its prevalence varies by country, it is generally low, estimated to between 0.71 and 2 *per* million person years[4]. Inflammation around the ear is a typical symptom that aids in prompt diagnosis[4]. HLH induced by RP is rare, with only a few case reports documented. Here, we report the diagnosis and treatment course of this patient as a case study.

CASE PRESENTATION

Chief complaints

A 71-year-old woman with fever visited the emergency room.

History of present illness

The patient presented with sore throat and cough, alongside fever and altered consciousness. The fever started 10 d prior to presentation and recurred multiple times daily.

History of past illness

The patient had taken antidepressants for major depressive disorder.

Personal and family history

The patient had no relevant family history.

Physical examination

Body temperature of the patient was 38.6 °C, and no other abnormal findings were detected during the initial physical examination.

Laboratory examinations

Initial testing revealed leukopenia (white blood cell count: 3890 /μL, normal range: 4000-10000 /μL) and anemia [hemoglobin (Hb): 9.9 g/dL, normal range: 12-16 g/dL]. Peripheral blood smear revealed leukopenia with left-shifted

maturation. Elevated levels of C-reactive protein (44.94 mg/L, normal range: 0-5.0 mg/L) and ferritin (1414 ng/mL, normal range: 13-150 ng/mL) were observed. The fluorescent antinuclear antibody titer was 1:1280, and the complement component 3 level was decreased (63.1 mg/dL, normal range: 90-180 mg/dL). Blood cultures showed no identifiable organisms, and viral markers for Epstein-Barr virus, cytomegalovirus and others did not yield significant results. The initial lesion around the ear resembled an infection caused by the herpes virus, so polymerase chain reaction was performed, but all results were negative.

Imaging examinations

Computed tomography (CT) revealed multiple enlarged lymph nodes (LNs) in the supraclavicular area and mediastinum, with necrotic changes observed in the left lower paratracheal LN (Figure 1). Additionally, ^{18}F-fluorodeoxyglucose (FDG) avid LNs in the left cervical, supraclavicular, and axillary areas were detected using FDG positron emission tomography/CT (PET/CT) (Figure 1).

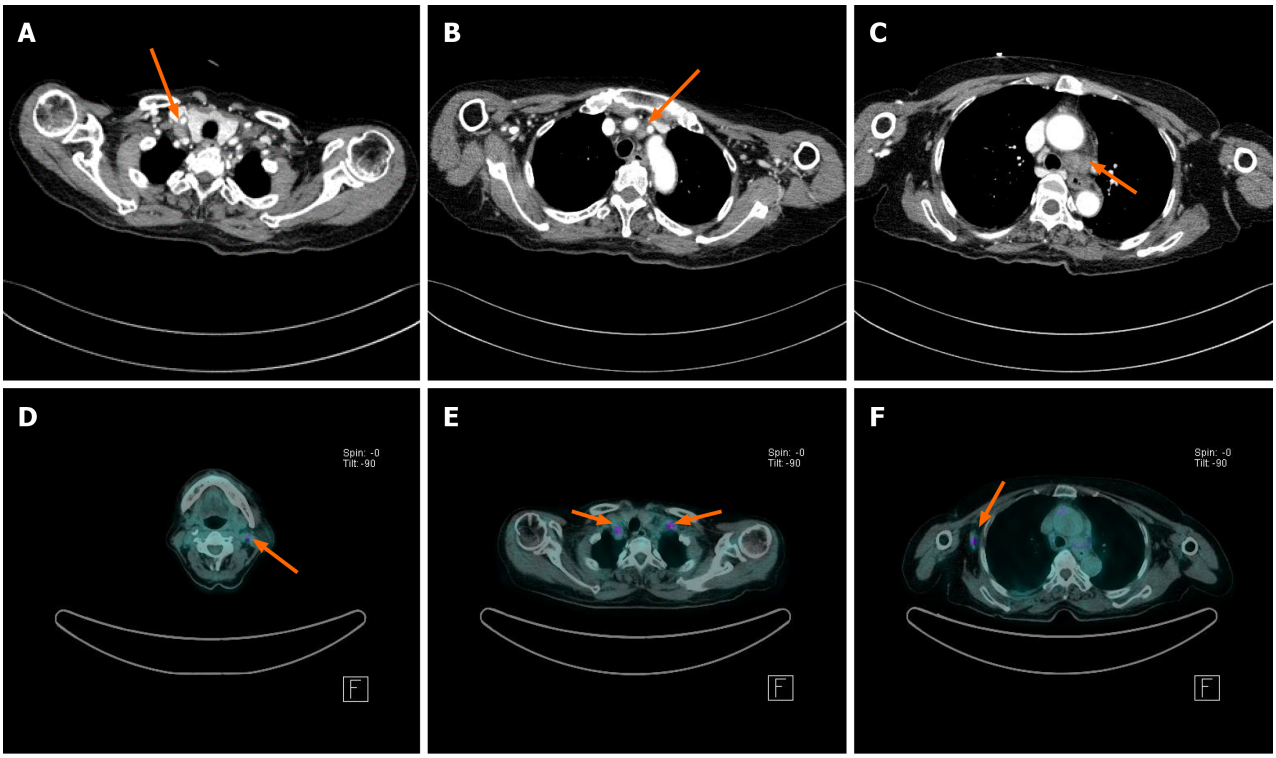

Figure 1 Computed tomography and fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography/computerized tomography findings. A-C: Enlargement of both supraclavicular and mediastinal lymph nodes was detected *via* computed tomography (CT); D-F: Positron emission tomography/CT revealed ^{18}F-fluorodeoxyglucose-uptake in the right cervical, both supraclavicular, and left axillary lymph nodes.

FINAL DIAGNOSIS

For diagnostic purposes, endobronchial ultrasound (EBUS) tissue examination was performed on the enlarged mediastinal LNs observed on the CT scan. The biopsy revealed only lymphocyte infiltration with no specific findings. However, on the second day of admission, redness and swelling were observed in both auricles, alongside ulcerative mucosal lesions on the soft and hard palates. Inflammation worsened in the auricles, and redness developed on the nasal ridge (Figure 2). A biopsy of the left auricle and histological findings confirmed RP (Figure 3). Furthermore, a bone marrow examination was conducted to evaluate the cause of pancytopenia (Hb: 9.0 g/dL, platelets: 75 × 10^3 /μL, and absolute neutrophil count: 0.56 × 10^3 /μL). Hemophagocytic histiocytes positive for immunophenotypes of CD68 were detected (Figure 4). To confirm HLH, tests that met the diagnostic criteria were performed. Hyperferritinemia worsened (11626.8 ng/mL, normal range: 13-150 ng/mL) and natural killer (NK) cell activity decreased (< 40.0 pg/mL, normal range: > 500 pg/mL). However, levels of soluble interleukin-2 receptor, triglyceride, and fibrinogen were within normal range. HLH diagnostic criteria were met by fever (≥ 38.5 °C), peripheral blood cytopenia, hemophagocytosis in bone marrow, low NK cell activity, and hyperferritinemia (> 500 ng/mL). Based on the absence of significant findings from laboratory tests for infections potentially triggering HLH, as well as from EBUS tissue examination for malignancies and other secondary causes, Thus, HLH triggered by the acute onset of RP was diagnosed.

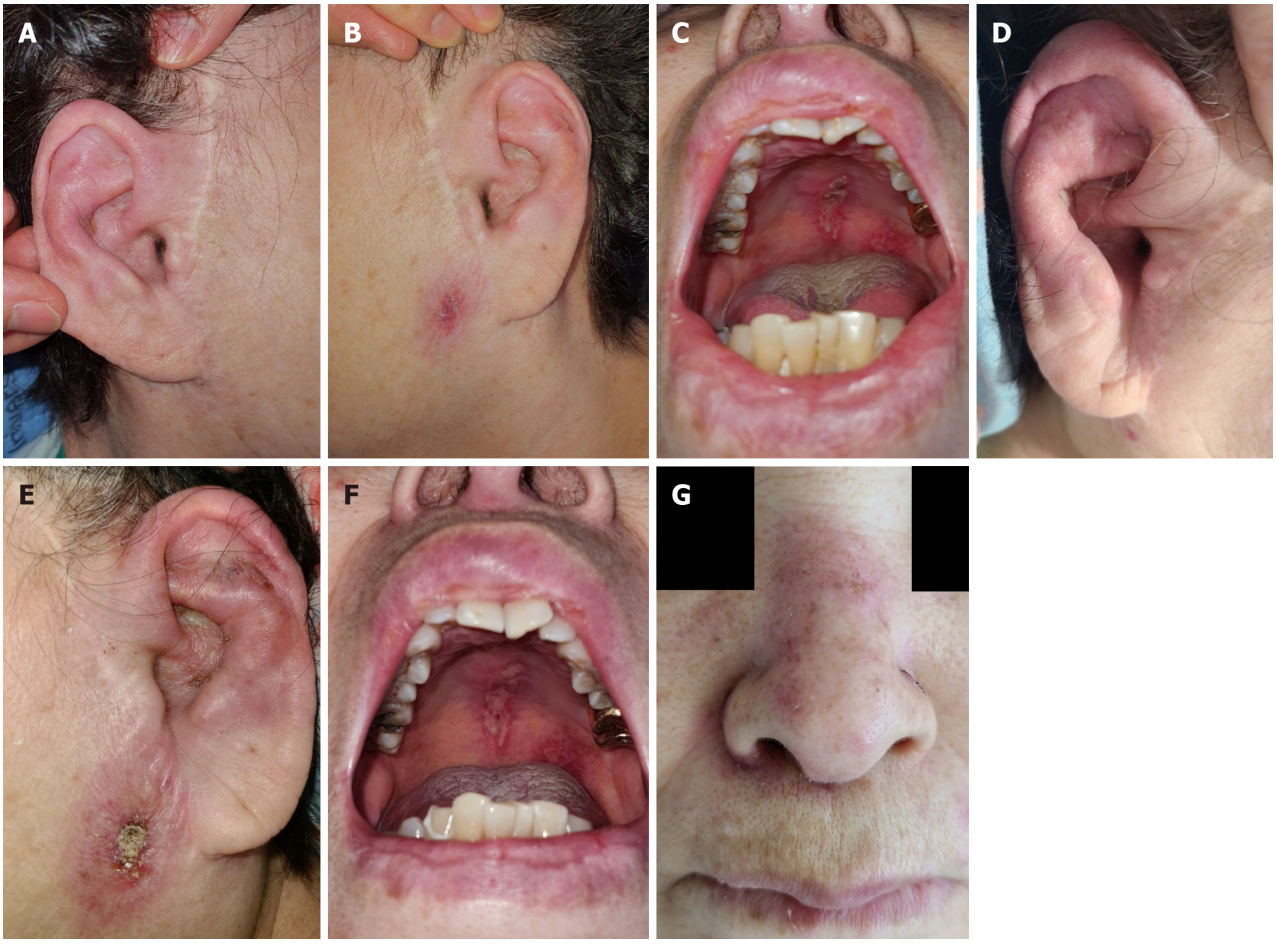

Figure 2 Photographs of a physical examination. A-C: Erythema and mild swelling on both auricles and ulcerative mucosal lesions on palates on the second day of admission; D-G: On day 10, erythema and swelling intensified on both auricles, with increased periauricular skin inflammation on the left side, and oral mucosal ulceration worsened, and erythema appeared on the nasal ridge.

TREATMENT

High-intensity treatment such as the HLH 2004 protocol was not feasible because of the patient's poor general condition. Instead, high-dose steroids (1 mg/kg of methylprednisolone) were administered to control RP. By the second day of steroid administration, the fever resolved, and her consciousness recovered. Inflammation in both the auricles and nasal ridge gradually subsided. The patient received 1 mg/kg of methylprednisolone for 3 weeks. Thereafter, the dose was reduced to 0.5 mg/kg and gradually tapered over 4 months. Azathioprine (50 mg twice daily) was added upon steroid dose reduction.

OUTCOME AND FOLLOW-UP

After 6 weeks of steroid treatment, a bone marrow examination exhibited resolution of hemophagocytosis, and pancytopenia and hyperferritinemia improved to normal. However, pneumonia developed while on azathioprine, leading to a reduction in dosage to 25 mg twice daily. Acute exacerbation of RP and HLH relapses did not occur; both conditions were well-controlled. Overall survival was 2 years and 10 months.

DISCUSSION

HLH is a rare, rapidly progressive, and life-threatening disease with a mortality rate of up to 40%. It is caused by immune reactions involving a severe inflammatory responses, cytokine overproduction, and hemophagocytosis, leading to fever, multiple organ dysfunction, shock, and even death. It can be classified into two types. Primary HLH is associated with genetic defects or abnormalities in immune function, primarily affection infants and young children; however, it can also be diagnosed in adults. Genetic defects in proteins responsible for cytotoxic function in T lymphocytes and NK cells can lead to dysregulated immune responses and excessive inflammation. Representative genes include *PRF1*, *UNC13D*, *STX11*, *RAB27A*[2,3]. Aggressive treatments such as hematopoietic stem cell transplantation are necessary, especially in

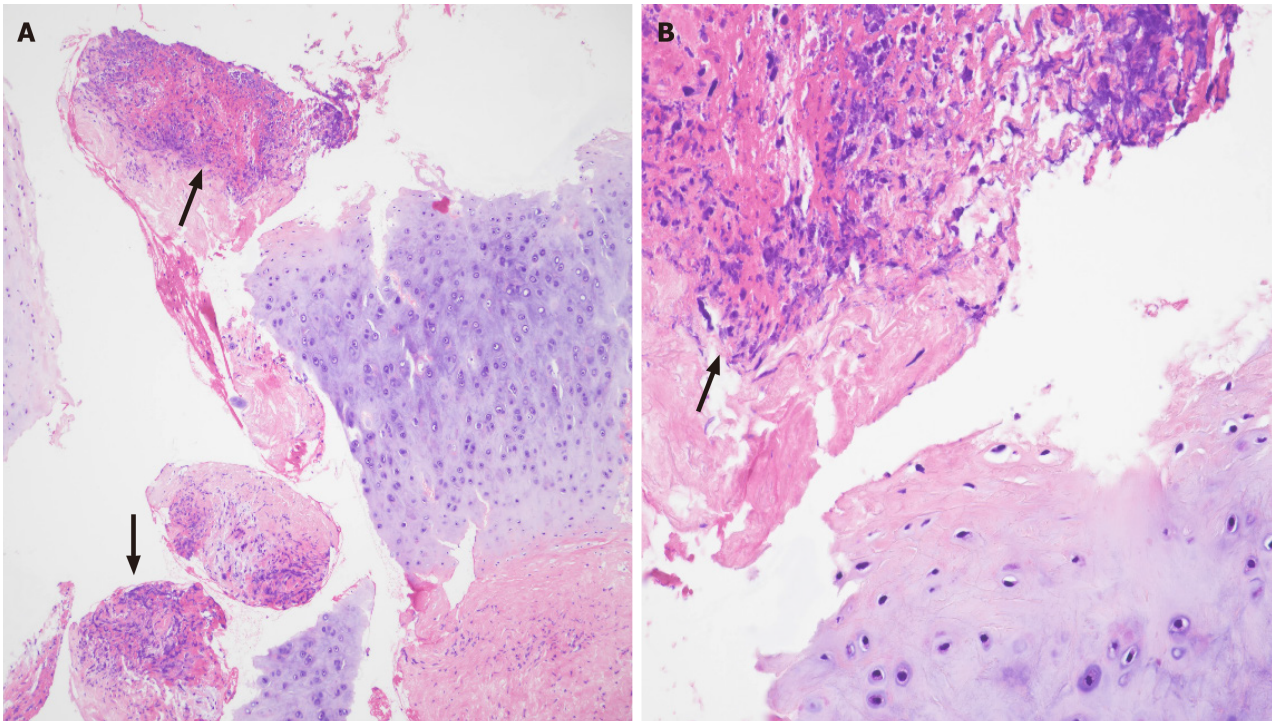

Figure 3 Histologic findings. Histologic findings of relapsing polychondritis of the ear. The fragmented biopsy specimen containing ear cartilage and adjacent fibrous tissue, with inflammatory infiltration and necrosis (arrows). A: Original magnification × 100; B: Original magnification × 400.

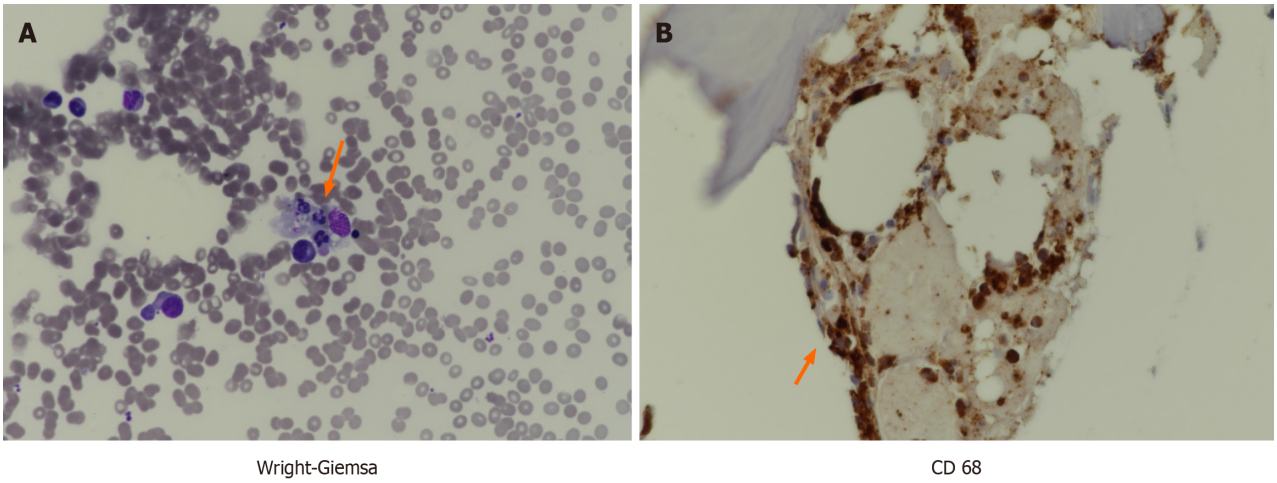

Figure 4 Bone marrow findings. A: Phagocytosis of blood cells is observed in the bone marrow stained with Wright-Giemsa (arrow); B: Cluster of differentiation 68 [CD68 (+)], a protein primarily expressed in cells such as macrophages, suggests excessive cellular activation and an inflammatory response.

cases with genetic predisposition. In contrast to primary HLH, where specific genetic mutations are the primary cause, secondary HLH typically arises from increased immune responses triggered by external factors such as underlying immune disorders, tumors, infections, or immunosuppressive agents. HLH frequently manifests in adults and is associated with various factors affecting immune function. Its pathogenesis involves genetic defects and abnormal activation or dysregulation of the immune system, leading to excessive activation of immune cells and tissue damage due to exaggerated inflammatory responses, cytokine storms, and other factors. In secondary HLH, a marked decrease in the cytotoxic function of lymphocytes and NK cells was observed, with excessive activation of the monocyte-phagocyte system being a characteristic feature[3]. Given the various triggering factors for HLH, recognizing presenting features and making a diagnosis can be challenging. The diagnostic criteria, including fever (≥ 38.5 °C), splenomegaly, cytopenia, ferritin level (> 500 ng/L), hypofibrinogenemia and/or hypertriglyceridemia, hemophagocytosis, low NK cell activity, and elevated soluble interleukin-2 receptor alpha level, lack sensitivity and specificity, especially in conditions such as lymphoma or sepsis[5,6]. Because the median survival period is < 2 months (1.8-2.2 months) without intervention, early treatment following accurate diagnosis is crucial. This patient was suspected to have secondary HLH owing to a confirmed preexisting disease at an advanced age. Genetic testing for accurate differential diagnosis was warranted, it is recommended to check genetic abnormalities, yet unavailable at our institution at the time.

RP, a rare autoimmune disease with an incidence rate of 3.5 cases *per* million *per* year, was identified as the trigger for HLH[7]. RP is characterized by inflammation of specific tissues and cartilage, affecting various areas including the ears, nose, airways, trachea, joints, and eyes, potentially spreading to involve the vasculitis, respiratory, and circulatory systems. It frequently occurs between 40 and 60 years old. The immune system attacks its own tissues, causing inflammation of the cartilage, primarily activated by T cells[7]. Excessive activation of CD4 + T cells, pivotal in immune regulation, is associated with RP onset and progression. Additionally, B cells and NK cells may contribute to RP pathogenesis. Diagnosis typically requires the presence of three or more symptoms: Bilateral auricular and nasal chondritis, nonerosive seronegative inflammatory polyarthritis, ocular inflammation, tracheal or laryngeal cartilage inflammation, and audiovestibular dysfunction[4]. As no established diagnostic blood test findings exist, the final diagnosis is based on clinical symptoms and tissue findings. Therefore, a comprehensive physical examination, based on the clinical symptoms, is crucial in diagnosing and formulating treatment plans. This examination should include assessing for abnormal signs such as swelling, erythema, and tenderness in areas in cartilage-rich regions such as the ears, nose, and joints. Furthermore, inflammation, such as conjunctivitis, keratitis, or scleritis, should be confirmed *via* eye examinations, whereas assessing symptoms such as respiratory sounds and coughing can indicate potential organ involvement. Although the exact mechanism of transition from RP to HLH remains elusive, dysregulated immune system activation in autoimmune diseases can induce tissue and organ inflammation by stimulating cytotoxic T and NK cell activation, consequently increasing the risk of HLH onset[3].

The treatment of HLH depends on symptom severity and the patient's overall condition. Typically, it involves medications such as etoposide, cyclosporine, and dexamethasone. If treatment response is inadequate or relapse occurs, hematopoietic stem cell transplantation is considered. In cases where HLH is associated with autoimmune diseases, treatment is based on addressing the primary disease[8]. RP treatment typically involves the use of immunosuppressants or anti-inflammatory agents to manage symptoms. If symptoms are not severe, anti-inflammatory medications such as colchicine or dapsone may be used. However, in cases of severe symptoms such as airway involvement or hearing loss, high-dose steroid administration or immunosuppressive agents such as cyclophosphamide, cyclosporine, or azathioprine are necessary[9]. Tocilizumab (an IL-6 targeted agent), rituximab (targeting CD20-positive B cells), and infliximab are being explored as biologic agents for RP treatment, functioning as monoclonal antibodies and TNF-α inhibitors.

CONCLUSION

In summary, we reported the diagnosis and treatment of HLH caused by RP in a patient presenting with a fever of unknown origin. Treatment involved administering steroids for RP at a dose of 1 mg/kg, followed by azathioprine. After the initial treatment, RP was not aggravated, and HLH did not relapse. RP diagnosis, enabling treatment, was not based on diagnostic tests and rather on clinical suspicion, prioritizing the observation of suspected lesions. Physician-conducted physical examination linked the two rare conditions, facilitating prompt diagnosis and treatment.

FOOTNOTES

Author contributions: Han MR wrote the manuscript; Cha S, Jang KY, and Kim NS collected and validated the data; Hwang JH and Jeon SY revised the manuscript; Lee CH was in charge of patient treatment and designed the manuscript; All authors have read and approved the final manuscript.

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