INTRODUCTION

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic infection characterized by fever, unproductive cough, and dyspnea. Nearly 20% of adults might carry \textit{P. jirovecii}\(^\text{2}\) and seroconversion of \textit{P. jirovecii}\(^\text{3}\) develops in 85% of infants by 20 months of age. \textit{P. jirovecii} infection typically presents as mild respiratory infection in healthy young children. However, typical PCP develops rapidly in a matter of days and has a mortality rate of 25–42% in non-human immunodeficiency virus (HIV)-positive immunocompromised patients when they...
do not receive the appropriate treatment as well as their underlying disease.3,6 One report showed that 9% of pediatric PCP inpatients had underlying primary immunodeficiency disease (PID).7 Therefore, prompt diagnosis of PCP and the underlying PID is crucial. However, diagnosis remains challenging in young infants with limited symptoms, particularly before the diagnosis of the immunocompromised state.

Herein, we report a case of a 5-month-old HIV-negative boy who presented with slowly progressing cyanosis for 3 weeks without fever or cough and was diagnosed with PCP and X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID).

2 | CASE HISTORY / EXAMINATION

A 5-month-old boy presented with a 3-week history of persistent cyanosis. He did not exhibit fever or respiratory symptoms, such as cough or rhinorrhea. The patient had continuous severe diarrhea for two months before admission.

His birth weight had been 2,092 g (−2.5 standard deviation [SD]), and he had been born at a gestational age of 38 weeks 5 days. He had not experience any episode of severe infection before the current admission. He had received the following vaccines: inactivated vaccines for Hib, PCV-13, Hepatitis B, diphtheria, pertussis, tetanus, polio, and three doses of the live attenuated rotavirus vaccine. According to the family medical history, his mother had been diagnosed with incontinentia pigmenti (IP) at 3 months of age. She had not had severe infections and discontinued medical follow-up. His maternal grandmother had suffered from refractory erythema and mouth ulcers from the age of 40 years.

On physical examination, the patient was found to be alert. His body temperature was 36.9°C, pulse rate was 160 bpm, blood pressure was 90/49 mmHg, respiration rate was 30 breaths per min, and oxygen saturation was 60% on room air. His body weight was 5,136 g (−3.2 SD). He presented with central cyanosis. His heart sounds were normal. Slight fine crackles were auscultated in his back. He had hepatosplenomegaly on abdominal examination. His skin was persistently dry due to anhidrosis, and his hair was sparse. The cyanosis and oxygen saturation improved with high-flow oxygen via a nasal cannula. Echocardiography revealed a normal heart structure and good cardiac function.

The patient’s laboratory data are described in Table 1. His white blood cell count was elevated, C-reactive protein was slightly elevated, venous blood gas contained normal levels of bicarbonate and carbon dioxide, serum immunoglobulin G (IgG) was low but IgM was high, and beta-D-glucan and KL-6 levels were markedly high. Chest X-ray showed a diffuse interstitial pattern, and chest computed tomography revealed ground-glass opacity in both lungs (Figure 1a,b), suggesting interstitial pneumonia. Polymerase chain reaction analysis of the patient’s respiratory secretions was positive for P. jirovecii. No data were indicative of other infections. Therefore, the patient was diagnosed with PCP. Additionally, his bone radiographs revealed fraying, indicating rickets.

3 | DIAGNOSIS AND TREATMENT

The patient was suspected to have XL-EDA-ID as an underlying immunocompromised condition due to his family medical history and elevated IgM level. Assessment of tumor necrosis factor-alpha (TNF-α) production by

| Table 1 | Laboratory data |
|---------|----------------|
| White blood count (µL) | 31,400 | 6,000–17,500 |
| Hemoglobin (g/dL) | 9.3 | 9.5–13.5 |
| Platelet count (×10⁴/µL) | 37.9 | 15–45 |
| Aspartate aminotransferase (U/L) | 37 | 25–68 |
| Alanine aminotransferase (U/L) | 11 | 13–55 |
| Lactate dehydrogenase (U/L) | 535 | 205–418 |
| Alkaline phosphatase (U/L) | 658 | 440–1600 |
| Total bilirubin (mg/dL) | 0.3 | 0.1–0.8 |
| Creatine kinase (U/L) | 78 | 43–321 |
| Ca (mg/dL) | 8.9 | 8.9–11.0 |
| CRP (mg/dL) | 0.78 | <0.3 |
| Immunoglobulin A (mg/dL) | 24 | 7–44 |
| Immunoglobulin G (mg/dL) | 112 | 290–960 |
| Immunoglobulin G2 (mg/dL) | 37.8 | 42–159 |
| Immunoglobulin G4 (mg/dL) | <2.0 | 0.3–10 |
| Immunoglobulin M (mg/dL) | 698 | 41–161 |
| Immunoglobulin D (mg/dL) | 0.2 | 0–1.1 |
| Immunoglobulin E (U/L) | 2 | <5 |
| KL−6 (U/mL) | 13,180 | <250 |
| Beta-D-glucan (pg/mL) | 582.7 | <11 |
| pH | 7.367 | 7.37 |
| PvCO₂ (mmHg) | 36.3 | 45 |
| HCO₃ (mmol/L) | 20.3 | 25 |

Abbreviation: CRP, C-reactive protein; PvCO₂, partial pressure of venous carbon dioxide.
lipopolysaccharide-stimulated CD14-positive cells was performed for XL-EDA-ID screening. We confirmed that reduction in TNF-α production in this patient was similar to the pattern observed in other XL-EDA-ID patients(Figure 2a). Nuclear factor-κB (NF-κB) essential modulator (NEMO) protein expression in lymphocytes was deficient, as previously described(Figure 2b). Genetic testing revealed an intron variant in the inhibitor of nuclear factor-kappa B kinase regulatory subunit gamma (IKBKG), c.768+5G>A(Figure 2c), as previously reported. This variant is known to be pathogenic in XL-EDA-ID, affecting splicing and resulting in truncated NEMO protein. Elevated IgM and anhidrotic skin are characteristic of XL-EDA-ID. Consequently, the patient was diagnosed with XL-EDA-ID.

The patient was treated with trimethoprim, sulfamethoxazole, and steroid pulse therapy for the PCP. He received intravenous IgG for agammaglobulinemia. He needed respiratory support initially, but his respiratory condition improved after three weeks. Oral supplementation of calcium and phosphorus improved bone fraying suggesting that the earlier diagnosis of rickets was secondary to malabsorption. Allogeneic hematopoietic cell transplantation (HCT) is potentially curative treatment for
severe cases of XL-EDA-ID, although a small number of cases have been reported.\textsuperscript{13} We performed HCT from an unrelated matched donor; however, this resulted in graft failure. The patient underwent a successful second HCT from his haploidentical father. The patient is alive and well, without any immunosuppressive drugs one year after HSCT.

### 4 | DISCUSSION AND CONCLUSIONS

This patient's case provided two important clinical insights. First, PCP in PID should be considered as a differential diagnosis in infants presenting with only gradually progressive cyanosis without inflammatory symptoms. Second, it is crucial to evaluate symptoms in all family members and offer detailed genetic counseling to patients with IP because the IKBKG variant can induce multiple associated symptoms.

This patient's case suggested that pediatric PCP in PID should be suspected even when patients present with only gradually progressive hypoxemia without fever or cough. The rates of fever and cough in pediatric PCP have been reported to be 95\% and 75\%, respectively, in HIV-negative children with PCP.\textsuperscript{13} It is possible that the patient did not exhibit fever because the underlying immunological dysfunction of XL-EDA-ID induces body temperature dysregulation.\textsuperscript{14} Regarding the rate of PCP progression, typical PCP in HIV-negative patients is associated with acute onset and rapid progression within a matter of days, while PCP in patients with HIV progresses within several days to weeks.\textsuperscript{15} However, this patient's PCP developed gradually over several weeks despite the presence of XL-EDA-ID.

Further, genetic counseling should be provided to every patient with IP because lethal infections can occur before XL-EDA-ID is diagnosed. XL-EDA-ID is characterized by immunodeficiency and ectodermal dysplasia due to NF-\(\kappa\)B inactivation. IKBKG encodes the NEMO protein. NEMO is a crucial component of the IxB kinase complex and regulates the NF-\(\kappa\)B signaling pathway, including TNF-\(\alpha\) receptors.\textsuperscript{16} NF-\(\kappa\)B inactivation affects T-cell and B-cell development and function in the immune system.\textsuperscript{17} Owing to this immunodeficiency, the first infection in XL-EDA-ID patients often results in death. It has been reported that early mortality related to XL-EDA-ID is increased, and 8\% of XL-EDA-ID patients have a history of PCP.\textsuperscript{16} Therefore, prompt diagnosis is required. Regarding the genotype-phenotype association, hypomorphic IKBKG variants can result in XL-EDA-ID in males, and amorphic IKBKG variants are lethal in males during development.\textsuperscript{16,18} Female IP patients have heterozygous hypomorphic or heterozygous amorphic variants of IKBKG. In the current case, the mother was unaware of the fact that her son could develop XL-EDA-ID. Lapse in medical follow-up of IP prevented her from receiving accurate guidance on managing IP and its importance in terms of medical history. Providing accurate information encourages close observation of the infant and helps promptly diagnose XL-EDA-ID and initiate treatment early. Genetic counseling for IP females is vital, particularly before pregnancy.

Moreover, detailed general family medical history is also essential. IKBKG variants induce various phenotypes. The cutaneous symptoms of this patient's grandmother suggested Behcet's disease, which is also associated with heterozygous IKBKG variants in female patients, relating to the lack of skewed X-chromosome inactivation. Two other families with similar presentations have also been reported.\textsuperscript{19,20} Therefore, careful and comprehensive support is necessary for families with XL-EDA-ID.

In conclusion, it is important to suspect PCP in PID in gradually progressive cyanotic infants, even without fever, cough, or relevant medical history. Family medical history is key to making the diagnosis. We suggest that genetic counseling should be provided to IP families in advance of pregnancy because XL-EDA-ID is often fatal in the first infection.

### ACKNOWLEDGMENTS

We thank the patient and his family for their permission to publish this manuscript.

### CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

### AUTHORS CONTRIBUTIONS

Miwako Toyohara and Yuko Kajiho contributed to the clinical management of the patient and the preparation of the manuscript. Both contributed equally to this work. Etsushi Toyofuku provided expert opinions and contributed to the making of the diagnosis. Chie Takahashi, Keiho Owada, Shoichiro Kanda, Yutaka Harita, and Akira Oka collected data and contributed to the making of the diagnosis and the clinical management of the patient. Kohsuke Imai, Hirokazu Kanegane, and Tomohiro Morio contributed to clinical management and provided expert opinions. Hideki Ohnisi and Taizo Wada performed laboratory analysis and provided expert opinions. All authors critically revised and approved the final manuscript.

### ETHICAL APPROVAL

The genetic examination was approved by the ethics committee of Gifu University.
CONSENT
Written informed consent was obtained from the parent of this patient to publish this case report and the accompanying images. All authors reviewed and approved the final manuscript.

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How to cite this article: Toyohara M, Kajiho Y, Toyofuku E, et al. An infant with X-linked anhidrotic ectodermal dysplasia with immunodeficiency presenting with Pneumocystis pneumonia: A case report. Clin Case Rep. 2021;9:e05093. https://doi.org/10.1002/ccr3.5093