Journal of Clinical Immunology (2019) 39:264–266
https://doi.org/10.1007/s10875-019-00626-3

LETTER TO EDITOR

Hemorrhagic Pneumonia as the First Manifestation of Anhidrotic Ectodermal Dysplasia with Immunodeficiency

Yuko Ichimiya[1,2] · Motoshi Sonoda[1] · Masataka Ishimura[1] · Shunsuke Kanno[1] · Shouichi Ohga[1]

Received: 16 November 2018 / Accepted: 7 April 2019 / Published online: 13 April 2019

Abbreviations

IL	Interleukin
LPS	Lipopolysaccharide
NEMO	Nuclear factor κB essential modulator
NF-κB	Nuclear factor κB
TNF	Tumor necrosis factor
XL-EDA-ID	X-linked anhidrotic ectodermal dysplasia with immunodeficiency

To the Editor:

X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID) is a primary immunodeficiency disease (PID) arising from the mutation of *IKBKG* that encodes NF-κB essential modulator (NEMO). Clinical expressions of the disease are characterized by abnormal teeth, hypohidrosis, sparse hair, and the immunological defects of impaired antibody response to polysaccharides, hypogammaglobulinemia, and impaired natural killer cell cytotoxicity. Patients are susceptible to infections with pyogenic bacteria, mycobacteria, parasites, viruses, and fungi [1]. Inflammatory bowel disease and autoimmunity are notable complications affecting the growth of pediatric patients.

We herein report a young infant who suddenly died of hemorrhagic pneumonia. Isolated pathogens of *Stenotrophomonas maltophilia* (*S. maltophilia*), *Klebsiella oxytoca* (*K. oxytoca*), and cytomegalovirus suggested an underlying immunodeficiency. Flow cytometric screening indicated the defective production of tumor necrosis factor (TNF)-α. Molecular autopsy determined the diagnosis of *IKBKG* deficiency in the family, which led to the neonatal diagnosis and preemptive care of a next-born sibling.

A 43-day-old male infant with hemoptysis and respiratory distress entered our emergency room. He was delivered via cesarean section because of non-reassuring fetal status at full term, weighing 2682 g. The newborn had meconium aspiration syndrome but was discharged from hospital without complication 5 days after birth. Neonatal mass-screening and regular health check were normal. The umbilical cord was separated over 21 days after birth. He was the first child of healthy non-consanguineous parents (Supplementary Fig. 1a). Family history was unremarkable, but skin macules were noticed on the forearms of the mother, aunt, and grandmother in the maternal side (Fig. 1a).

On admission, the afebrile infant exhibited tachycardia (165/min), tachypnea, retraction (60/min), and 69 mmHg of systolic blood pressure. SpO_2 was 97% on receiving 10 L/min of mask oxygen. Capillary refill time was over 2 s. The cold legs showed livedo reticularis and spotty pigmentations (Fig. 1b). Blood clots stained the mouth. He had eczema on the face, large pigmented nevi on the lower lip, sparse hair and eyebrows, but no dysmorphisms. Auscultation revealed poor aeration but no heart murmur or adventitious breath sounds. Blood tests showed a leukocyte count of 31.910×10^9/L with 18% neutrophils, 67% lymphocytes, 5% monocytes, a hemoglobin concentration of 8.1 g/dL, and a platelet count of 33×10^9/L. Aspartate aminotransferase (157 U/L, rr 24–43), lactate dehydrogenase (2854 U/L, rr 190–365), creatine kinase (987 U/L, rr 43–270), and C-reactive protein (5.65 mg/dL, rr < 0.04) levels were increased. Slightly elevated D-dimer levels (1.7 μg/mL, rr 0.15–1) heralded severe coagulopathy. Venous blood gas analysis showed respiratory acidosis (pH 7.229, PCO_2 59.6 mmHg) and elevated lactate levels (28 mg/dL, rr < 18). Cefotaxime was immediately administrated. Positive pressure ventilation and transfusions led to a transient improvement of desaturation, but pulmonary bleeding required

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-019-00626-3) contains supplementary material, which is available to authorized users.

✉ Masataka Ishimura
ischii@pediatr.med.kyushu-u.ac.jp

[1] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

[2] Emergency and Critical Care Center, Kyushu University, Fukuoka, Japan

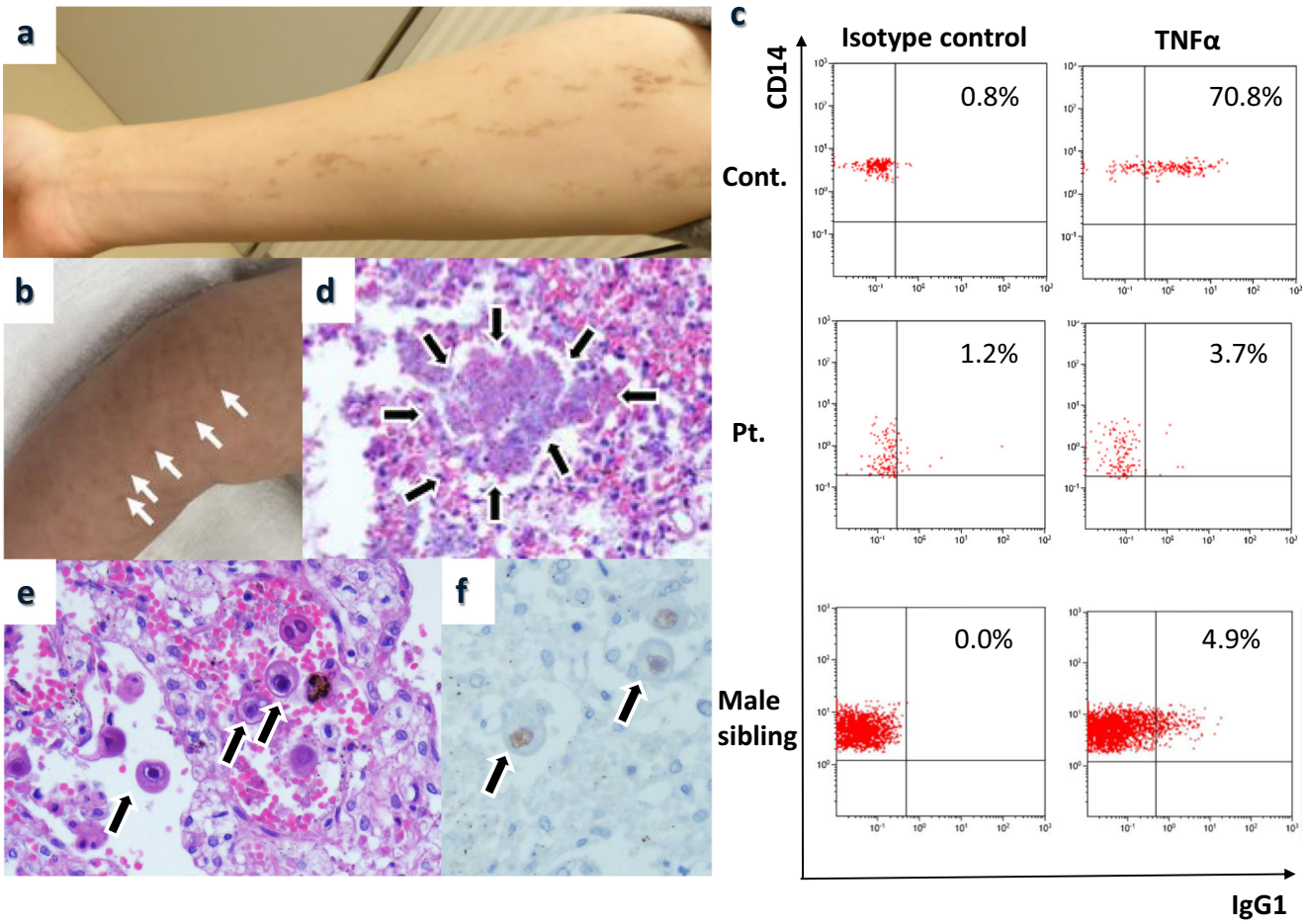

Fig. 1 **a** Skin macules on the right forearm of the mother. **b** Skin pigmentation on the leg of the patient (white arrow). **c** Flow cytometric analysis of intracellular TNF-α production of monocytes in response to LPS. Intracellular staining for TNF-α shows its expressing monocytes are diminished to 3.7% compared with controls assessed by flow cytometry, as previously established. **d** Postmortem histopathology of the lung tissue shows diffuse alveolar bleeding and frequently encountered Gram-negative rods (black arrow), but few infiltrations of inflammatory cells. **e**, **f** Cytomegalovirus-infected airway epithelial cells (black arrow)

extracorporeal membrane oxygenation 15 h after admission (Supplementary Fig. 2). *S. maltophilia* and *K. oxytoca* were isolated from blood, sputum, and stool cultures; trimethoprim/sulfadiazine and anti-mycotic agents were then added with the introduction of polymyxin B-immobilized fiber column. Despite the intensive care, he died of massive bleeding 36 h after admission.

During the intensive care, flow cytometric analyses indicated defective TNF-α production from lipopolysaccharide (LPS)-stimulated monocytes with healthy controls (3.7% vs. 70.8%, Fig. 1c). $CD14^+$ mononuclear cells did not release TNF-α after stimulation with LPS alone, or LPS plus 10 or 100 U/ml of interferon-γ (data not shown). Serum levels of interleukin (IL)-6 and IL-8, but not TNF-α, were elevated during the treatment (Supplementary Fig. 2). Histopathology of the autopsied lungs showed diffuse alveolar bleeding and Gram-negative rods, few unremarkable infiltrations of inflammatory cells (Fig. 1d, Supplementary Fig. 1b). Cytomegalovirus infection was determined in the immunohistochemical staining (Fig. 1e, f). Delayed separation of the umbilical cord and skin pigmentations prompted us to complete the mutation analysis of *IRAK4*, *MYD88*, and *IKBKG* genes [1]. He had a reported pathogenic hemizygous mutation (c.1167dupC, exon 10, p.Glu390ArgfsTer5) in *IKBKG* gene [2], but no mutation in *IRAK4* or *MYD88* gene that reached the diagnosis of XL-EDA-ID (Supplementary Fig. 1c). His healthy mother, aunt, and grandmother received the diagnosis of incontinentia pigmenti because of sharing the heterozygous mutation in *IKBKG* gene, pigmented macules, and normal monocytic TNF-α production (Supplementary Figs. 1c and 1d). A newborn male received the neonatal diagnosis of XL-EDA-ID and has been carefully observed on antimicrobial prophylaxis and immunoglobulin replacement (Fig. 1c, Supplementary Fig. 1c).

The early diagnosis and management of XL-EDA-ID are challenging because of a wide spectrum of phenotypes. Some patients with c.1167dupC, p.Glu390ArgfsTer5 resulted in fatal infections in infancy and others with the mutation received successful bone marrow transplantations [2]. In the young

infant with hemorrhagic pneumonia, delayed separation of the umbilical cord, skin pigmentation, and rapid screening for TNF-α production narrowed the diagnosis of innate immune defect. His mother's female relatives shared the mutation and a skin manifestation of incontinentia pigmenti. The basis of aggressive pneumonia accounts for the genetic effect and multiple infections.

Patients with XL-EDA-ID are prone to infections with various pathogens including encapsulated bacteria, nosocomial microbes, and mycobacteria. Dysmorphism and recurrent infections are not evident in early infancy. Hypomorphic mutations in *IKBKG* are associated with varied expressions in affected boys [2]. Amorphic mutation of *IKBKG* results in the full expressions of female incontinentia pigmenti. Therefore, the recognition of incontinentia pigmenti in the mother is critical for the neonatal diagnosis of XL-EDA-ID. Numerous stimuli via Toll-like receptor, IL-1 receptor, and TNF receptor make use of common interacting and adaptor molecules to induce the classical NF-κB pathway in mammals. Immune defects of EDA-ID originate from the impaired activation of NF-κB. Many patients present with infections within a few months of life, when maternal IgG provides a modest ability of protection against bacteria. It suggests an innate, but not, adaptive immune defect depending on NF-κB activation [3]. Most of reported cases with c.1167dupC showed severe infections. A case with the *IKBKG* mutation showed reduced expression of NEMO protein and decreased cytokine responses to lipopolysaccharide [2].

The major concern is the rapid progression of hemorrhagic pneumonia. A protease produced by *S. maltophilia* degrades collagen fibers and fibronectin in fibroblasts and endothelial cells, leading to the destruction of the alveolar microvessels of the lung [4]. In the review of all six reported cases of *S. maltophilia*-induced hemorrhagic pneumonia in childhood, three leukemic children resulted in the rapid demise of pneumonia and three newborn cases survived. Infections with commensal bacteria are an important cause for non-relapse mortality of leukemic patients. Scheich et al. [5] have recently reported that *S. maltophilia* colonization was found in 20 of 291 patients (6.9%) and that the colonized patients had a poor survival due to higher non-relapse mortality. The aggressive course in this infant allowed no time to assess the effect of alternative antimicrobial therapy. The histopathology for the autopsied lungs indicated the florid bacterial dissemination suggestive for poor host response. *K. oxytoca* and cytomegalovirus infections would argument the lung injury with alveolar hemorrhage to respiratory failure. In this context, the rapid demise of hemorrhagic pneumonia and sepsis appeared to chiefly depend on the impaired immunological function of patients.

The present case exemplified no promising therapy for hemorrhagic pneumonia in young infants with PID. Hematopoietic stem cell transplantation is the curative treatment for the infection proneness of XL-EDA-ID [2]. This family emphasizes the significance of newborn screening of inborn errors of immunity to infection for the complete cure of disease.

Acknowledgments We sincerely thank Dr. Noriyuki Kaku, Dr. Yoshitomo Motomura, Dr. Katsuhide Eguchi, Dr. Akira Shiraishi, Dr. Kanako Ishii, Prof. Hidetoshi Takada, and Prof. Tomoaki Taguchi for valuable advices. We are grateful to Dr. Yui Nozaki and Prof. Yoshinao Oda for pathological diagnosis. This work was supported in part by Practical Research Project for Rare/Intractable Diseases (JP16ek0109099) and Grant-in-Aids (JP16ek0109098h0002) from the Japan Agency for Medical Research and Development (AMED) and the Research on Measures for Intractable Diseases Project and Health and Labor Sciences Research Grants (Research on Intractable Diseases) from the Ministry of Health, Labour and Welfare.

Authors' Contribution The contributions of each author are as follows. YI, MS, MI, and SO were the principal investigators, taking primary responsibility for the paper. MS completed the immunological studies and genetic analysis. MI established the immunological screening, quality control of the tests, and genetic counseling.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

References

1. Picard C, Bobby GH, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018;38:96–128.
2. Tono C, Takahashi Y, Terui K, Sasaki S, Kamio T, Tandai S, et al. Correction of immunodeficient associated with NEMO mutation by umbilical cord blood transplantation using a reduced-intensity conditioning regimen. Bone Marrow Transplant. 2007;29:801–4.
3. Orange JS, Levy O, Geha R. Human disease resulting from gene mutations that interfere with appropriate nuclear factor-kappaB activation. Immunol Rev. 2005;203:21–37.
4. Windhorst S, Frank E, Georgieva DN, Genov N, Buck F, Borowski P, et al. The major extracellular protease of the nosocomial pathogen *Stenotrophomonas maltophilia*: characterization of the protein and molecular cloning of the gene. J Biol Chem. 2002;277:11042–9.
5. Scheich S, Koenig R, Wilke AC, Lindner S, Reinheimer C, Wichelhaus TA, et al. *Stenotrophomonas maltophilia* colonization during allogeneic hematopoietic stem cell transplantation is associated with impaired survival. PLoS One. 2018;13:e0201169.