CASE REPORT

MIRAGE Syndrome Due to a de novo SAMD9 c.2944C > T (p.Arg982Cys) Variant: a Case Report and Relevant Literature Review

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SUMMARY

Background: MIRAGE syndrome is a rare autosomal dominant genetic disorder.

Methods: We studied a 15-month-old girl with growth retardation and refractory respiratory infections.

Results: The patient had thrombocytopenia and was positive for Epstein-Barr virus, cytomegalovirus IgM and IgG, and herpes simplex virus type I and II IgG. The genomic analysis reported a heterozygous de novo SAMD9 c.2944C > T (p.Arg982Cys) pathogenic variant. She improved after antibiotic treatments, but finally died due to severe recurrent infection.

Conclusions: Patients with MIRAGE syndrome could have various clinical presentations. Infections from mixed pathogens are common, which require adequate coverage for bacteria, viruses, and fungi.


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KEYWORDS
MIRAGE syndrome, SAMD9, infection, developmental delay

LIST OF ABBREVIATIONS
SAMD9 - sterile alpha motif domain containing 9

CASE PRESENTATION

On January 28th, 2019, a 15-month-old girl presented with refractory respiratory infections. She was born at 40 weeks gestation from healthy non-consanguineous parents. The pregnancy and vaginal delivery were uneventful. The mother denied any previous history of pregnancy or miscarriage. After the birth, the patient was diagnosed as small for gestational age. Once the child reached 13 months, she began to have recurrent fevers with coughing and wheezing. Approximately 40 days ago, the girl developed a cough and shortness of breath, with increased stool frequency 4 - 5 times/day. She visited several local hospitals. A computed tomography scan showed bilateral multiple pulmonary infiltrations and consolidations. The blood
tests were positive for Epstein-Barr virus, cytomegalovirus IgM and IgG, and herpes simplex virus type I and II IgG. Routine blood counts showed normal white blood cell count (8.6 x 10^9/L), anemia, and thrombocytopenia (platelet count 55 x 10^9/L). Bone marrow biopsy revealed active bone marrow hyperplasia, but with decreased number of granulocytes (mainly decreased metamyelocytes with maturation disorder). Despite treatments with multiple antibiotics (cefepime, ceftriaxone, fusidic acid, imipenem, rifampicin, and linezolid), antiviral treatments (vidarabine, peramivir), methylprednisolone, and intravenous gamma globulin, she still had a persistent fever up to 40°C. The patient was then transferred to our hospital.

At our hospital admission, the girl had episodic cough and shortness of breath. Her vital signs were temperature 39.6°C, heart rate 110 - 124 beats/minute, blood pressure 86/54 mmHg, and respiration rate 26 - 35 breaths/minute. The head circumference, body weight, and length were 45 cm, 7.4 kg, and 71.4 cm, respectively, which were significantly lower than the 90% of children in the same age and gender group. She was awake and alert. There was no rash, petechia, abnormal pigmentation in the skin, or cyanosis. The head appearance was normal but with large ears. She cried with tears. Small movable lymph nodes were palpable in the neck and axillary areas. Lung auscultations revealed crackles and wheezing bilaterally. Her external genitalia showed normal female appearance. She could not walk independently.

The laboratory tests showed white blood cell count 8.2 x 10^9/L, neutrophil percentage 45.6%, platelet count 97 x 10^9/L, hemoglobin 98 g/L, and C-reactive protein 32 mg/L. Blood gas analysis revealed pH 7.36 mmHg, PO_2 91 mmHg, PCO_2 42.4 mmHg, oxygen saturation 97%, and lactate 2.0 mmol/L. Peripheral blood smear showed normal white blood cell morphologies, variable red blood cell shapes and sizes, with enlarged central pale zone. There were 28% neutrophils (decreased), 44% lymphocytes (decreased), 14% monocytes (increased), 0% eosinophils (decreased), 0% basophils, and 14% atypical lymphocytes (increased). The serum procalcitonin level increased to 3.9 ng/mL. Lung computed tomography scan showed bilateral lung infiltrations, ground-glass opacities, and multiple patchy shadows (Figure 1A, 1B). She immediately received treatment with ceftriaxone.

Additional laboratory tests showed that the respiratory pathogen panel, bronchoalveolar lavage fluid culture, and acid-fast staining were all negative. Plasma Epstein-Barr virus-DNA and cytomegalovirus-DNA were negative. The Epstein-Barr virus IgM was negative but IgG was positive. The cytomegalovirus IgM was negative but IgG was positive. The herpes simplex virus type I and type II IgG were positive. The tuberculosis test (T-SPOT) was negative. Immunoglobulin tests showed IgA 0.9 g/L (increased), IgM 1.85 g/L, IgG 14.2 g/L (increased), total IgE 55.07 ku/L. Complement tests showed C3 1.27 g/L, C4 0.24 g/L, CH50 60 U/mL. CD cells showed CD16*CD56* 6.72% (absolute count 247.06/mm^3), CD3^+ 86.32% (absolute count 3,173.3/mm^3), CD19^+ 6.43% (absolute count 236.35/mm^3), CD4^+ 39.60% (absolute count 1,445.90/mm^3), CD8^+ 46.75% (absolute count 1,718.71/mm^3), CD4^+CD8^+ 0.85. Both the proteinase 3- and myeloperoxidase-enzyme-linked immunosorbent assay were positive (36.6 RU/mL and 57.4 RU/mL, respectively). The alveolar lavage fluid rhinovirus nucleic acid test was positive. The mycoplasma DNA test was 4.5 x 10^3 copies/mL. The hematoxylin and eosin stain and Wright’s stain of alveolar lavage fluid showed a large number of neutrophils and a small number of histiocytes and epithelial cells. The girl still had persistent fever after ceftriaxone treatment for 7 days. The antibiotic was changed to cefepime-sulbactam, and then switched to meropenem and azithromycin 3 days later. Her body temperature returned to normal range 2 days later. A repeat laboratory test showed procalcitonin level of 0.05 ng/mL. Repeat lung computed tomography scan and bronchoscopy also showed improvements.

We performed the genomic DNA sequencing analysis, with the whole exome sequencing test [1]. Her chromosome karyotype was 46, XX. A heterozygous de novo pathogenic variant c.2944C > T (p.Arg982Cys) in the exon 3 of the SAMD9 gene in chromosome 7 (locus 92732467) was detected (Figure 1C). Further genomic DNA sequencing in the parents did not show a similar genetic pathogenic variant. Therefore, a diagnosis of MIRAGE syndrome due to a de novo pathogenic variant in the SAMD9 gene was diagnosed in the patient.

After clinical improvements, the girl was discharged with oral cefixime and nebulized budesonide. During the clinical follow-up visits, the girl had intermittent fever, which was resolved after antibiotic treatments. However, at the age of 2.5 years old, she had a recurrent fever and was admitted to the local hospital. She received antibiotics again but with poor response. The girl finally died.

**DISCUSSION**

MIRAGE syndrome occurs due to the gain-of-function pathogenic variants in the SAMD9 gene [2]. There is no clear relationship between genotype and phenotype [3]. Here, we report a patient with MIRAGE syndrome and a de novo pathogenic variant c.2944C > T (p.Arg982Cys) in the SAMD9 gene. The same pathogenic variant was reported in three other unrelated patients previously (Table 1) [4, 5]. In 2017, Buonocore et al. reported eight children with MIRAGE syndrome [4]. Two of these children carried the pathogenic variant c.2944C > T (p.Arg982Cys) in the SAMD9 gene. Both of them were evaluated initially due to growth retardation and severe testicular dysfunctions. They had the karyotype of 46, XY with female or ambiguous genitalia, and adrenal insufficiency, but only one of them was reported to have thrombocytopenia and anemia. Both of them died with-
MIRAGE Syndrome Due to a de novo SAMD9 Variant

Table 1. Clinical characteristics of patients diagnosed as MIRAGE syndrome with the pathogenic variant c.2944C > T (p.Arg982Cys) in the SAMD9 gene.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Karyotype</th>
<th>Age at delivery</th>
<th>Presenting chief complaints</th>
<th>Growth delay</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Adrenal insufficiency</th>
<th>Infection</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buonocore et al., 2017 [4]</td>
<td>46, XY</td>
<td>34 weeks</td>
<td>growth delay, female genitalia</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>died at 3 months</td>
</tr>
<tr>
<td></td>
<td>46, XY</td>
<td>31 weeks</td>
<td>growth delay, ambiguous genitalia</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>died at 9 months</td>
</tr>
<tr>
<td>Kim et al., 2018 [5]</td>
<td>46, XY</td>
<td>31 weeks</td>
<td>respiratory distress, hypotension</td>
<td>yes</td>
<td>mild, then resolved</td>
<td>yes, then resolved</td>
<td>yes</td>
<td>yes</td>
<td>died at 4 months</td>
</tr>
<tr>
<td>Present case</td>
<td>46, XX</td>
<td>40 weeks</td>
<td>refractory respiratory infection</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>died at 2.5 years</td>
</tr>
</tbody>
</table>

Figure 1. Chest X-ray (A) and computed tomography scan (B) showed bilateral lung infiltrations, ground-glass opacities, and multiple patchy shadows.

The whole exome sequencing test (C) revealed a heterozygous de novo pathogenic variant c.2944C > T (p.Arg982Cys) in the patient but not her parents.

in one year of age, presumably due to severe infections. Kim et al. reported another MIRAGE syndrome with the c.2944C > T (p.Arg982Cys) pathogenic variant in the SAMD9 gene in a child (46, XY), who presented initially with respiratory distress and hypotension [5]. The patient was found to have growth retardation, severe adrenal insufficiency, and skin hyperpigmentation. His mild thrombocytopenia and anemia improved spontaneously 1 month after delivery. The patient ultimately died from septic shock. Our patient had the karyotype of 46, XX and female genitalia who was evaluated initially due to refractory pulmonary infection. Laboratory tests showed severe thrombocytopenia with mild anemia. Although we did not test her adrenal function, she was not likely to have severe adrenal insufficiency, since the adrenal gland showed normal morphology under the ultrasound examination and she did not have skin hyperpigmentation and her blood chemistry tests were within normal limits. Our present case and these previous cases suggest that patients with MIRAGE syndrome might present to the hospital with different initial symptoms. It is important to remind the clinicians to rule out MIRAGE syndrome in suspected patients.

Infection, especially recurrent respiratory infection, is one of the most important factors affecting the prognosis of MIRAGE syndrome [2,6]. Affected children often die from refractory infection with multiple mixed pathogens during the follow-up period [6-8]. In addition to bacteria, viruses and fungi were frequently detected as infections leading to death. Therefore, when treating patients with MIRAGE syndrome, clinicians should administer antibiotics, antivirals, and antifungals with ade-
quate and broad coverage for all possible pathogens. In addition, intravenous immunoglobulin infusion should be considered in patients with low immunoglobulin levels.

CONCLUSION

We report a case of MIRAGE syndrome with a de novo c.2944C > T (p.Arg982Cys) heterozygous pathogenic variant in the SAMD9 gene. Patients with MIRAGE syndrome could have various clinical presentations. Clinicians should rule out this syndrome in appropriate patients. In addition, infections from mixed pathogens were common in affected patients. Adequate antibiotic treatments should cover bacteria, viruses, and fungi.

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Availability of Data and Materials:
The datasets used and analyzed during the current study are not publicly available due not all of the researchers’ wish to share the data with public at present, but available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate:
The research protocol was assessed and ethics approval was obtained from the Research Ethics Committee of Children’s Hospital of Fudan University. Informed consent was obtained from a parent or other legal guardian of the individual participant included in the study. All the methods were performed in accordance with the relevant guidelines and regulations.

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

References: