

Case Report

MIRAGE syndrome with recurrent pneumonia probably associated with gastroesophageal reflux and achalasia: A case report

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Abstract. Aspiration pneumonia is a common complication of myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome. However, the detailed clinical course of aspiration pneumonia in neonates and infants diagnosed with this disorder remains unclear. We report a case of a 2-yr-old girl diagnosed with MIRAGE syndrome during the early neonatal period. The patient developed 3 episodes of aspiration pneumonia until 4 mo of age, and this complication was attributed to esophageal hypoperistalsis secondary to achalasia and gastroesophageal reflux. Enteral feeding via a duodenal tube effectively prevented further episodes of aspiration pneumonia in this patient.

Key words: MIRAGE syndrome, gastroesophageal reflux, esophageal hypoperistalsis, aspiration pneumonia

Introduction

Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome was first reported by Narumi and Amano *et al.* in 2016 (1).

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“MIRAGE” is an acronym for the aforementioned features/conditions that characterize this disorder. The prognosis of patients with MIRAGE syndrome varies depending on patients' susceptibility to invasive infections. A previous study reported that 6 of 11 patients with this condition died of infections (1, 2) and that 4 of 9 patients who survived > 3 mo with a documented clinical course (1) manifested recurrent aspiration pneumonia during infancy and childhood. To date, no report available in the literature has described the detailed clinical course of MIRAGE-induced aspiration pneumonia.

This case report highlights that recurrent aspiration pneumonia in patients with MIRAGE

syndrome may be attributed to esophageal hyperperistalsis secondary to achalasia and to gastroesophageal reflux (GER) and that duodenal tube placement can effectively prevent recurrent aspiration pneumonia.

Case Report

The patient's mother was a 31-yr-old gravida 1, para 0 who conceived following successful infertility treatment. Ultrasonography performed during pregnancy revealed severe and gradually progressive fetal intrauterine growth retardation (IUGR) based on estimation of crown-rump length (-1.8 standard deviation [SD] in length at 20 wk, -2.1 SD at 22 wk, and -3.9 SD at 30 wk of gestation). Disruption of blood flow through the umbilical cord necessitated an emergency cesarean section at 32 wk and 2 days' gestation.

The patient was born in poor condition, with 1 and 5 min Apgar scores of 3 and 7, respectively. She weighed 776 g (-3.9 SD) at birth, with a length of 32.5 cm (-3.8 SD) and a head circumference of 24.5 cm (-2.5 SD). Artificial respiration was initiated after birth to maintain a stable respiratory status. She was transferred to our hospital within a few hours postpartum. Physical examination performed on admission showed generalized skin pigmentation, and her external genitalia were normal (Fig. 1). No other physical abnormalities were observed. Artificial respiration was withdrawn without surfactant therapy a day after birth.

Laboratory investigations are shown in the Table 1. Elevated plasma renin activity (120 ng/ml/h) and elevated levels of adrenocorticotrophic hormone (1290 pg/ml) were observed, although her electrolytes were within normal limits. The adrenal glands were not visualized on ultrasonography. Urinary steroid profiling revealed low levels of $\Delta 5$ steroid metabolites, suggesting congenital adrenal hypoplasia (2). Her platelet count was low at birth ($3.5 \times 10^4/\mu\text{l}$) and decreased to $1.9 \times 10^4/\mu\text{l}$ the following day, necessitating platelet transfusion. Polymerase

chain reaction analysis for the *SRY* gene showed negative results, which was subsequently confirmed by chromosomal analysis showing the 46, XX karyotype. Based on the combination of IUGR, congenital adrenal hypoplasia, and thrombocytopenia, she was diagnosed with MIRAGE syndrome, which was confirmed by genetic analysis of the *SAMD9* gene, which revealed a previously reported heterozygous missense mutation c. G1376A p.R459Q (Fig. 2) (1).

Nasogastric tube feeding with breast milk was initiated on the 4th day of birth. Frequent watery diarrhea was observed after enteral feeding was introduced. Regular formula feeding was initiated at 7 mo of age owing to lack of breast milk. The patient developed vomiting a few hours after receiving regular formula; therefore, she received only elemental formula thereafter. Poor weight gain was observed despite an intake of 100 kcal/kg/d. She weighed 3.4 kg at 17 mo of age (Fig. 3).

The patient developed 4 episodes of aspiration pneumonia when exclusive breastfeeding was continued until 7 mo of age (see below). The first episode of aspiration pneumonia occurred the day after oral intake was first attempted at 30 d of age (her modified gestational age was 36 wk, 4 d), and oral feeding was discontinued after this episode. Presumptive episodes of aspiration pneumonia also occurred at 73 and 105 d of age when a nasogastric tube had already been placed. Antibiotics (cefotaxime) successfully treated all episodes of aspiration pneumonia, although their use exacerbated the patient's diarrhea. Blood, cerebrospinal fluid, and urine cultures during these 3 episodes of pneumonia yielded negative results. Chest computed tomography performed at 3 mo of age revealed multifocal inflammatory infiltrates, which supported the diagnosis of aspiration pneumonia (Fig. 4). The fourth episode of aspiration pneumonia occurred secondary to issues with the duodenal tube at 5 mo of age.

An upper gastrointestinal contrast study



Fig. 1. Physical examination findings at birth showing completely feminized genitalia in this patient.

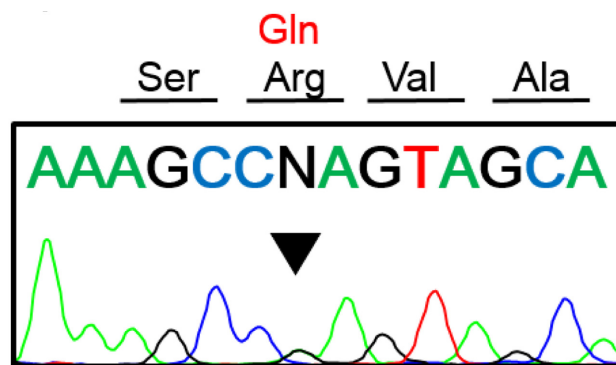


Fig. 2. Chromatogram showing the *SAMD9* mutation identified in this patient (c.G1376A, p.R459Q). The arrowhead shows the mutated nucleotide.

Table 1. Laboratory data obtained 1 day after birth

WBC	10.3 × 10 ⁵ /µl	TP	5 g/dl	ACTH	1290 pg/ml
Hb	18.1 g/dl	Alb	3.1 g/dl	Cortisol	4.7 µg/dl
Plt	3.5 × 10 ⁴ /µl	BUN	6.8 mg/dl	DHEA-S	38 µg/dl
		Cr	0.54 mg/dl	Aldosterone	181 pg/ml
		IgG	287 mg/dl	PRA	120 ng/ml/h
		IgM	2 mg/dl		
		HCO ₃ ⁻	21.7 mmol/l		

Samples were collected before steroid replacement therapy. ACTH: adrenocorticotrophic hormone, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, DHEA-S: dehydroepiandrosterone-sulfate, Hb: hemoglobin, HCO₃⁻: bicarbonate, Ig: immunoglobulin, Plt: platelets, PRA: plasma renin activity, TP: total protein, WBC: white blood cells.

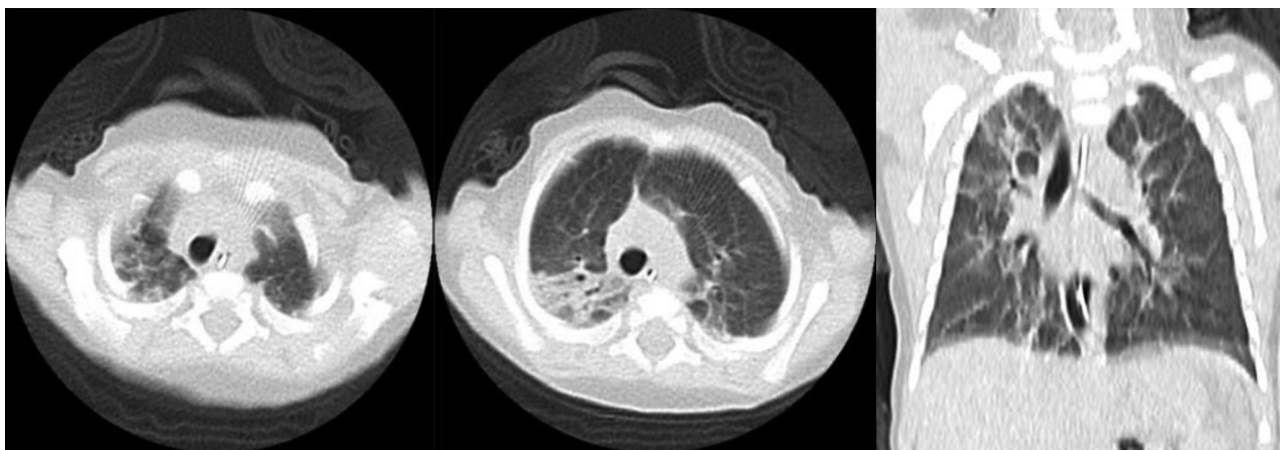


Fig. 4. Chest computed tomography (CT) scan performed at 3 mo of age showing multifocal inflammatory infiltrates and segmental atelectasis.

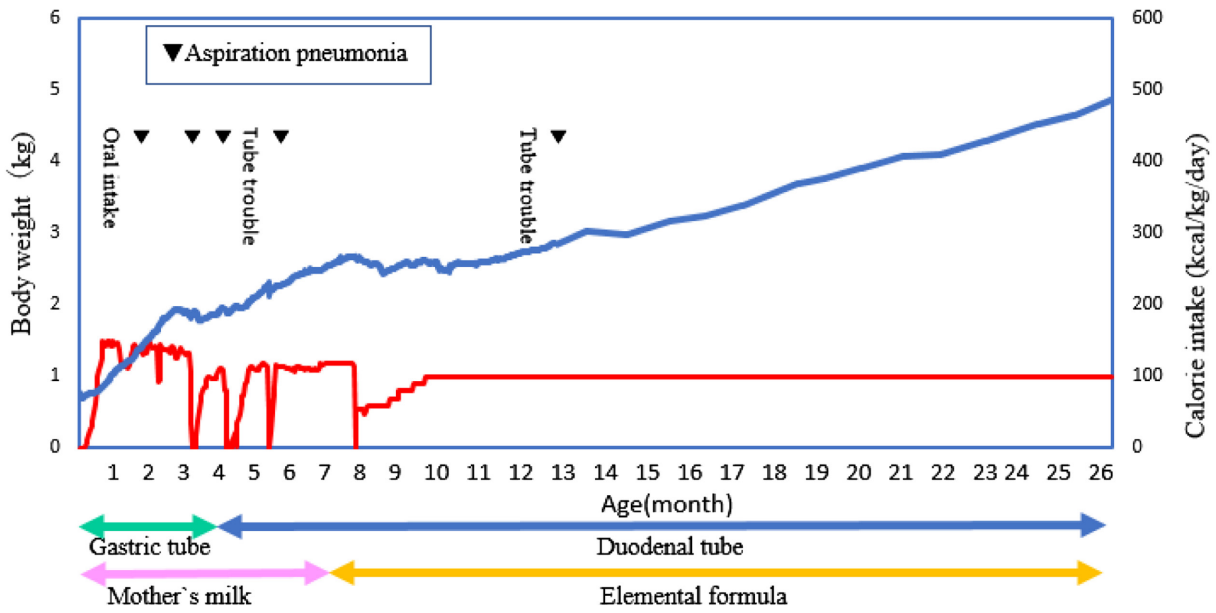


Fig. 3.

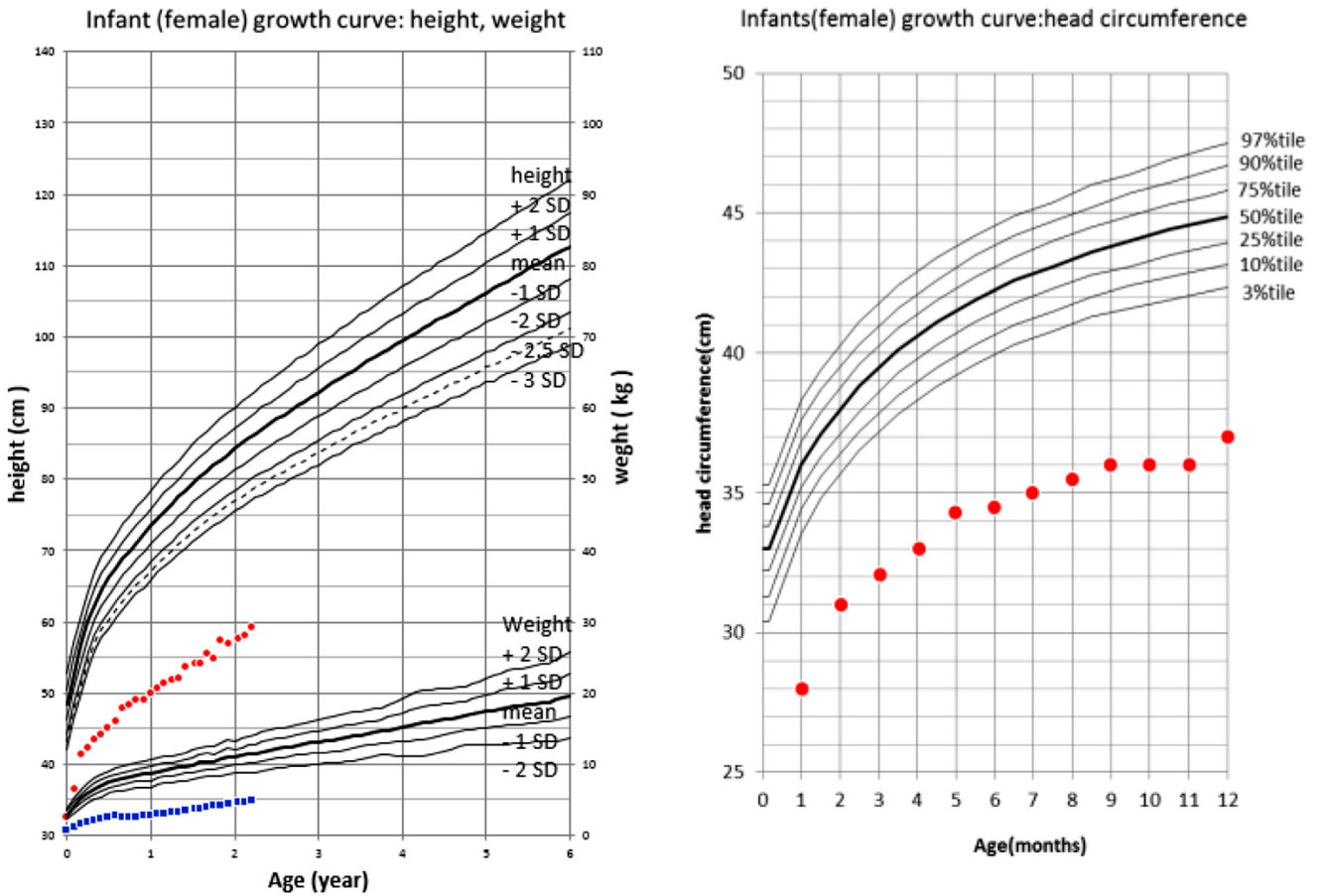


Fig. 5.

performed at 3 mo of age revealed esophageal hypoperistalsis with enlargement. Absence of peristalsis and failure of relaxation of the lower esophageal sphincter led to a high index of clinical suspicion for achalasia. The gastric tube that had been placed for enteral feeding was replaced with a duodenal tube, which prevented further episodes of aspiration pneumonia, except the single episode secondary to the use of the duodenal tube, as described earlier. The contrast study did not reveal GER; however, we speculated that GER had been present in early infancy because duodenal tube placement at 4 mo of age prevented any further episodes of aspiration pneumonia. An upper gastrointestinal contrast study was performed at 30 mo of age to confirm the diagnosis of achalasia again, and GER was documented at this age as well. Duodenal tube placement has continued to prevent aspiration pneumonia until the patient's current age of 2 yr and 6 mo.

Based on the findings of a previous report, the patient received 6 courses of intravenous immunoglobulin by the age of 1 yr to prevent severe invasive infections (1). Severe infections did not occur before or after intravenous immunoglobulin therapy. It is difficult to confirm the exact effect of this therapy in the present case; however, this therapy is unlikely to have altered the clinical course in this patient.

Hormonal replacement therapy for adrenal insufficiency was initiated at 1 d of

age. Hydrocortisone was administered at a dose of 100 mg/m²/d and was subsequently tapered. A maintenance regimen consisting of a combination of hydrocortisone (15 mg/m²/d) and fludrocortisone (0.02 mg/d) was administered at 2 yr and 6 mo of age. By 30 mo of age, the patient presented with 7 episodes suggesting adrenal insufficiency, clinically manifested with cyanosis, irritability, hypotonicity, and poor activity, which improved with an increase in the hydrocortisone dosage (50–100 mg/m²/d). Four of these episodes were associated with identifiable triggers of adrenal insufficiency (worsening diarrhea, infant formula feeding, bathing, and dental treatment under local anesthesia).

The only treatments rendered for myelodysplasia were a platelet transfusion at 1 d of age and erythrocyte transfusion at 61 d of age. A complete blood count (CBC) obtained thereafter did not reveal cytopenia. This improvement in the CBC with age was also documented previously (3, 4).

The patient had severe growth retardation. Her height, weight and head circumference were shown in Fig. 5. The patient showed poor progress in psychomotor and language development. Her developmental level at 27 mo of age was equivalent to that of a 5- to 6-mo old child. Head magnetic resonance imaging performed at 8 mo of age revealed ventricular enlargement without intracranial hypertension.

Fig. 3. Patient's clinical course. This graph shows the body weight (in blue) and nutritional status (in red) associated with episodes of aspiration pneumonia. Three episodes of aspiration pneumonia occurred until 4 mo of age. The first episode occurred the day after oral intake was initiated at 1 mo of age. The other episodes occurred at 3 and 4 mo of age. The etiology of aspiration pneumonia was identified as GER and achalasia at 4 mo of age, after which gastric tube feeding was switched to duodenal tube feeding. Aspiration pneumonia did not occur after 4 mo of age except an episode when the duodenal tube was removed. Enteral feeding was completely discontinued because antibiotic therapy for pneumonia caused severe diarrhea. The patient received artificial formula for the first time at 7 mo of age owing to lack of breast milk, which triggered episodes of loose stool and acute adrenal failure, necessitating complete discontinuation of enteral nutrition.

Fig. 5. Growth charts of the patient showing significant growth retardation. Height is in red in the chart on the left, weight in blue in the chart on the left, and head circumference in red in the chart on the right. Her height was 59.3 cm (−8.8 SD) and weight was 4.8 kg (−5.2 SD) at 26 mo of age.

Discussion

We suspected that recurrent aspiration pneumonia in this patient was attributable to achalasia and GER. Enteral feeding via a duodenal tube effectively prevented aspiration pneumonia.

Recurrent pneumonia is a serious complication that affects the prognosis in patients with MIRAGE syndrome, particularly if the condition is accompanied by achalasia, a rare condition with an incidence of 1 in 100,000. Achalasia is characterized by an abnormality in lower esophageal sphincter relaxation and esophageal dilatation most often causing aspiration pneumonia (5). In the first report describing MIRAGE syndrome (1), 4 of 11 patients developed recurrent aspiration pneumonia. Among these 4 patients, GER was detected in 1 and achalasia in 2 patients. Information regarding the remaining patient was unavailable. Reportedly, a 12-yr-old boy who received gastric tube feeding showed GER without achalasia. Of the 2 patients diagnosed with achalasia who received duodenal tube feeding, 1 died following gastric hemorrhage at 7 mo of age and the other died following complications of achalasia (which had been clinically misdiagnosed as the triple A or adrenal insufficiency, alacrima, and achalasia syndrome) at 2 yr and 10 mo of age. Achalasia may be a presenting feature of this syndrome because it is not a common condition as stated earlier. Peroral endoscopic myotomy is increasingly being used as first-line therapy for achalasia (5).

It is unclear whether GER is a characteristic finding in patients with MIRAGE syndrome. GER can occur even in healthy infants until 2 yr of age depending on their relative maturity (6–8). Patients with mental impairment also may present with GER (9). We speculate that MIRAGE syndrome is associated with an increased risk of GER because nearly all cases of MIRAGE syndrome reported in the available literature have described severe IUGR and

mental impairment in these patients.

The clinical spectrum of MIRAGE syndrome is expanding. Recent reports have described patients presenting only or primarily with myelodysplasia and IUGR without adrenal failure (10, 11). From a clinical perspective, clinicians should consider this condition in the differential diagnosis in patients presenting with clinically severe recurrent aspiration pneumonia with achalasia, particularly in those with other symptoms suggestive of this syndrome. A diagnostic approach for esophageal hypoperistalsis/achalasia and GER, which predisposes to recurrent aspiration pneumonia, is essential for optimal therapeutic management of patients with this syndrome.

Conclusion

GER and achalasia are common complications of MIRAGE syndrome. Appropriate evaluation of these complications is important for optimal management of patients with MIRAGE syndrome.

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