Tittle: Report of case from Saudi Arabia with Infantile systemic hyalinosis suspected initially as Spinal muscular atrophy

Abstract:
We present a case of infantile systemic hyalinosis (ISH) in a 5-month-old male child born to consanguineous parents via in vitro fertilization (IVF). The child exhibited symptoms such as fever, diarrhea, abdominal distension, and joint contractures, prompting hospital admission. Genetic testing revealed homozygous deletion of exons 7 and 8 in the SMN1 gene, confirming spinal muscular atrophy (SMA). Notably, a previous child in the family was diagnosed with SMA type 1. This case underscores the rarity of ISH in Saudi Arabia and highlights the challenges of managing rare genetic disorders in pediatric patients.

Introduction:
In vitro fertilization (IVF) has revolutionized reproductive medicine, offering hope to couples facing infertility challenges and those at risk of passing on genetic disorders to their offspring.(1) SMA and infantile systemic hyalinosis (ISH) are two rare genetic conditions that may necessitate the use of IVF due to familial predisposition or infertility issues.(2) SMA, characterized by progressive muscle weakness and atrophy, results from mutations in the survival motor neuron 1 (SMN1) gene.(3) ISH, on the other hand, manifests as joint contractures, skin lesions, and gastrointestinal complications due to mutations in the CMG2 (capillary morphogenesis gene 2) or ANTXR2 (anthrax toxin receptor 2) genes.(4)

The utilization of IVF in cases of SMA and ISH offers families the opportunity to undergo genetic screening and preimplantation genetic diagnosis (PGD) to identify and select embryos unaffected by these debilitating conditions.(5) This approach not only allows for the prevention of disease transmission but also provides hope for the birth of healthy offspring.(6) However, IVF procedures come with their own set of ethical, social, and psychological implications, necessitating careful consideration and counseling for prospective parents.(7)

This introduction aims to provide an overview of IVF and its role in addressing genetic disorders such as SMA and ISH, highlighting the challenges and advancements in reproductive medicine. (8)

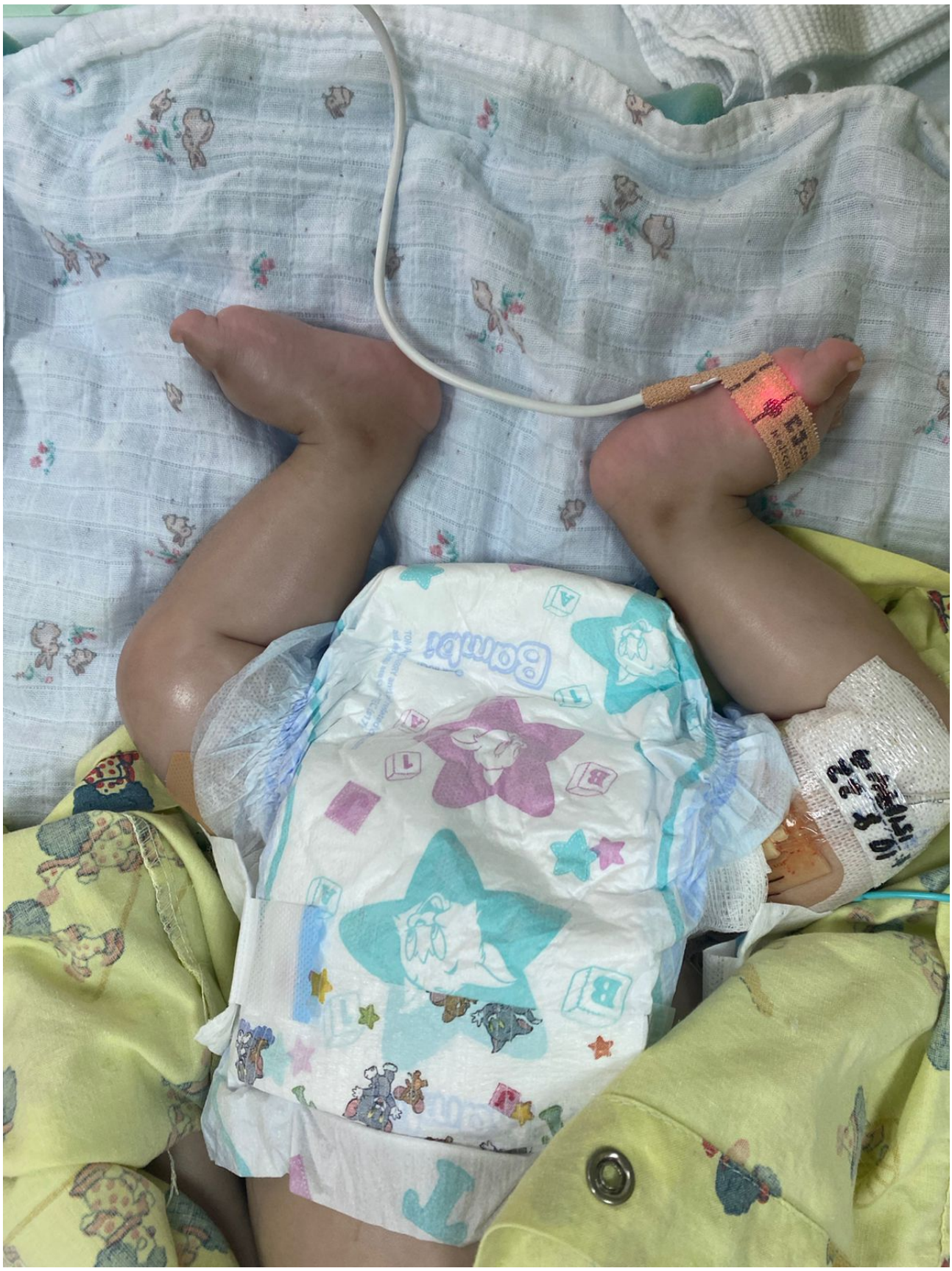
Case Report:
A 5-month-old male child born out of a consanguineous marriage was delivered via in vitro fertilization (IVF) pregnancy due to a family history of spinal muscular atrophy (SMA). The child presented with a 2-week history of fever and diarrhea, occurring up to 10 times per day, with stools described as moderate to large in amount, yellow, very watery, and occasionally mixed with mucus. Abdominal distension was noted, leading to admission to a private hospital for 13 days under the diagnosis of gastroenteritis.

The patient exhibited decreased activity and oral intake, along with multiple brownish raised lesions over bony prominences. Additionally, he developed difficulty in moving his limbs, resulting in severe flexion joint contractures. Severe developmental delay with hypotonia was observed; the child was unable to roll over or hold his head, or grasp objects. Initially breastfed, the child was supplemented with aptamil, and later transitioned to lactose-free formula and then to novalac.

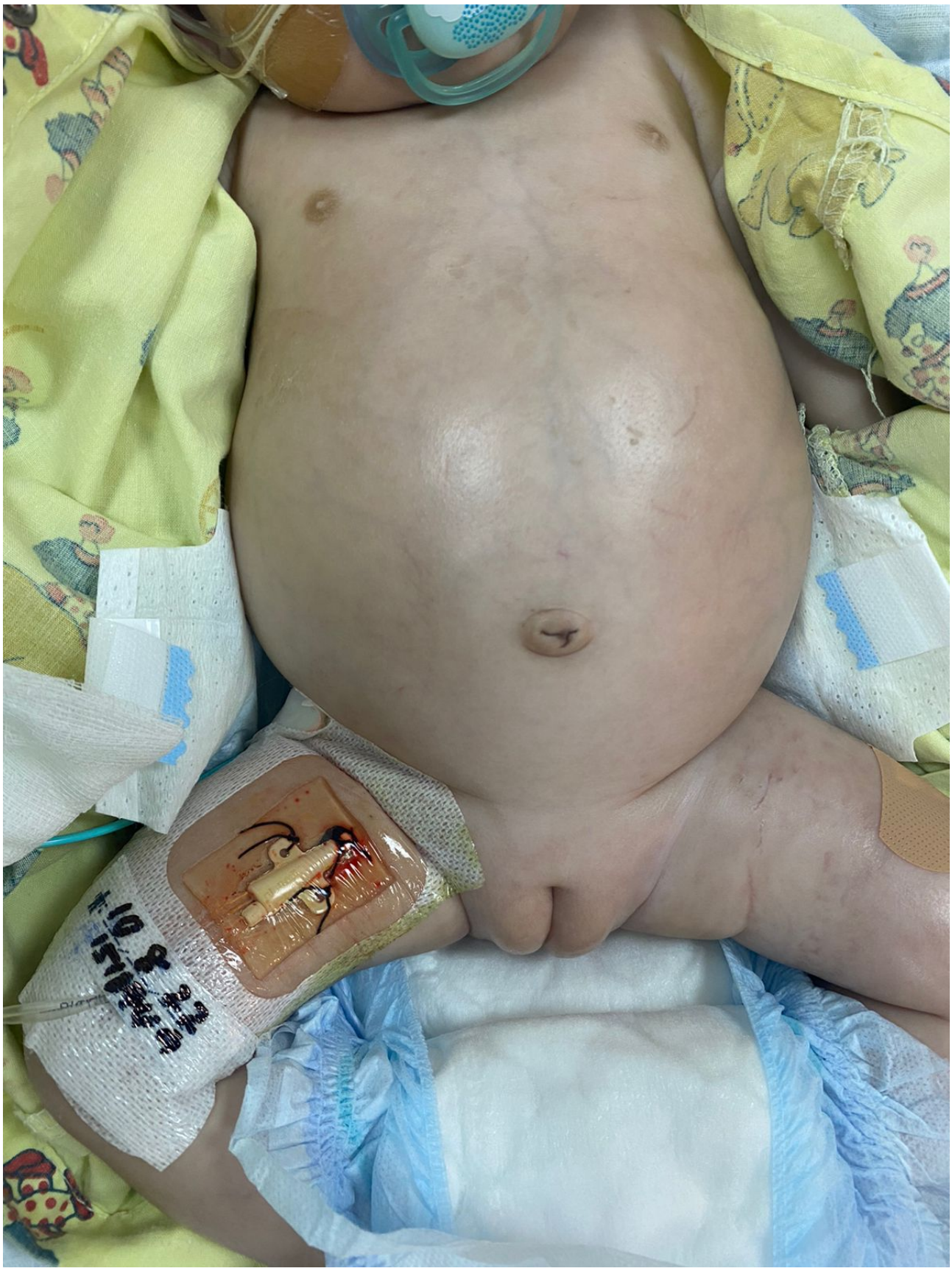
Family history revealed a similar presentation in the eldest daughter, diagnosed with SMA type 1, who passed away at 1 year and 8 months in 2010. Genetic testing using DNA specimens showed a deletion of exons 7 and 8 in both alleles of the SMN1 gene (homozygous). Another child, a 9-year-old boy born via IVF pregnancy, was reported as healthy and medically free.

The patient was admitted to the Pediatric Intensive Care Unit (PICU) with a diagnosis of fluid-responsive hypovolemic shock with metabolic acidosis and clinical sepsis. A skin fungal infection was also noted. Hypoxic respiratory failure secondary to Parainfluenza Virus 3 necessitated non-invasive ventilation (high flow nasal cannula). Treatment included administration of Fluconazole, Vancomycin, Meropenem, and Tazocin from 12th to 16th July.

Physical Exam:
- Vital signs: Temperature 38.3°C, Heart rate 182 bpm, Respiratory rate 60 breaths per minute, Oxygen saturation 98% on room air, Blood pressure 91/67 mmHg. The child appeared hypoactive with moderate respiratory distress.
- Fontanelles were open and flat, with a rash noted in the right neck (site of previous line, now removed).
- Cardiac examination revealed audible first and second heart sounds with no murmur.
- Capillary refill was less than 2 seconds, with palpable pulses bilaterally and warm extremities.
- Respiratory assessment showed grunting, nasal flaring, and equal bilateral air entry with transmitted sounds.
- The abdomen was distended but soft, tender (eliciting crying upon palpation), with a diaper rash present.
- Musculoskeletal examination revealed clenching of both hands with mild spasticity, movement observed in lower limbs, and edema noted in the lower limb.

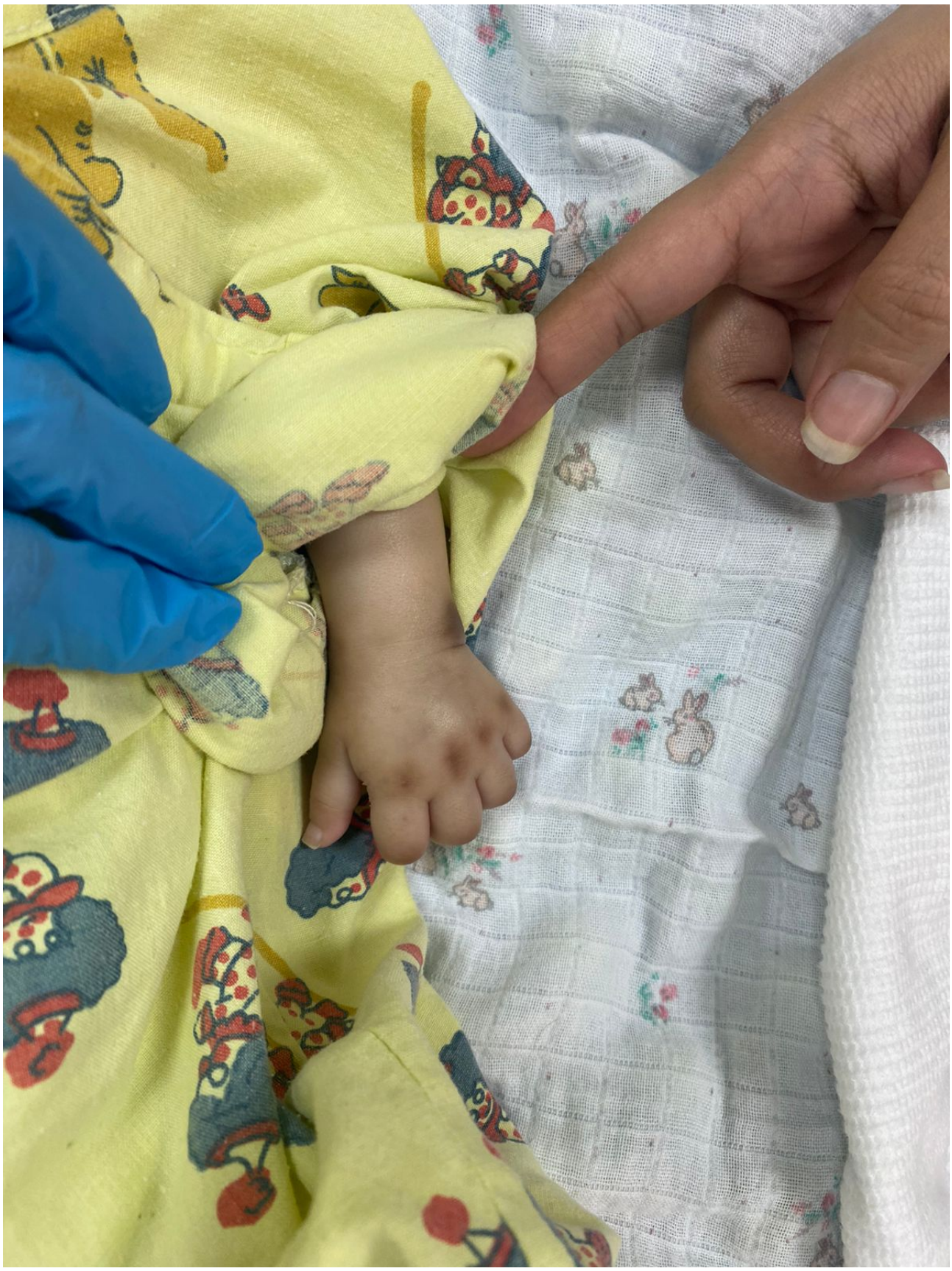


This is picture of both legs, showing frog like position, hyperpigmentation of the skin at ankle joint on both legs, and edematous of both feet and showing joint contractures.



This is picture of abdominal distension, and femoral line on the right leg.

This is picture of right hand showing joint contractures and hyperpigmentation of skin at metaphalangeal and proximal interphalangeal all joint



This is picture for the left hand showing contracture of the joint, and hyperpigmentation of skin at metaphalangeal joint

Discussion:
The discussion highlights the clinical features, histopathology, genetics, and management of infantile systemic hyalinosis (ISH) in the context of the presented case, which involves a co-occurrence of ISH with spinal muscular atrophy (SMA). ISH, described in detail by Landing in 1986, is part of the spectrum of infantile stiff skin syndromes, which also includes Winchester's syndrome, congenital fascial dystrophy, and juvenile hyaline fibromatosis (JHF).

The pathogenesis of hyalinosis syndromes, including ISH, remains obscure, but studies have shown increased chondroitin synthesis in skin fibroblasts in systemic hyalinosis, along with abnormalities in the metabolism of type III collagen. There has been debate among authors regarding the existence of separate disorders, such as JHF and ISH, with attempts made to differentiate between them.

Clinical features of ISH typically manifest in early life and include failure to thrive, painful joint contractures, diffuse nodular thickening of the skin, gingival hyperplasia, severe chronic diarrhea, and recurrent sepsis, often leading to death before the age of 3. Histopathology and electron microscopy of skin tissue are crucial for establishing the diagnosis, with characteristic findings of homogeneous, eosinophilic amorphous material in the papillary and reticular dermis, which is PAS positive.

Genetic mapping has identified chromosome 4q21.21 and deletion mutations in CMG2 (capillary morphogenesis gene 2) and anthrax toxin receptor 2 (ANTXR2) in patients with both JHF and ISH, suggesting they belong to the same disorder spectrum.

Management of ISH remains challenging, with no well-established treatment guidelines. Breakthrough infections, particularly bacterial pneumonia and diarrhea, require hospitalization and antibiotic therapy. Some reports have suggested mild improvement in joint mobility with d-penicillamine, while surgical excision of troublesome nodules may be considered, although recurrence is common. Aggressive management of joint contractures with dedicated physiotherapy is essential to maintain ambulation.

In conclusion, ISH remains a poorly understood disorder with diagnostic and therapeutic challenges for physicians. Further research is needed to elucidate its underlying pathophysiology and explore potential treatment strategies.

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