Delayed Presentation of Respiratory Symptoms and Prolonged Survival in Homozygous α3 Integrin Deficiency

Interstitial lung disease with nephrotic syndrome and junctional epidermolysis bullosa is caused by biallelic mutations in the integrin gene *ITGA3* and is associated with death in infancy. We describe a variant of this syndrome with delayed presentation of symptoms and prolonged survival.

Keywords: Epidermolysis bullosa, ILNEB syndrome, Nephrotic syndrome.

Integrins play a vital role in cellular interactions. Interstitial lung disease with nephrotic syndrome and junctional epidermolysis bullosa (ILNEB syndrome) is an autosomal recessive disorder caused due to deficiency of integrin α3. Of the reported 9 cases [1-6], most patients with homozygous *ITGA3* mutations died in infancy. We present a variant of ILNEB syndrome with delayed presentation of renal and life-threatening respiratory symptoms and prolonged survival past early childhood.

A 9-year-old female child, second born to third degree consanguineous parents, was admitted with complaints of insidious onset breathlessness for 6 months. She was apparently normal till 2 years of age when she developed blistering skin lesions that healed with scarring. She complained of passing foamy, frothy urine, and periorbital puffiness on and off from 4 years of age but was never treated with any chronic medications. Renal symptoms had not progressed for last five years. She also had a history of excessive tearing of eyes and loss of eye lashes and eyebrows. The antenatal and perinatal history was uneventful and developmental milestones were appropriate for age. Examination revealed growth retardation, normal mentation, superciliary madarosis, epiphora, scarring alopecia of scalp, icthyosis in both arms, forearms, and legs, toe nail dystrophy, healed atrophic scars over body, hyperlinearity of palms and soles, and clubbing of digits **(*Web Fig.* 1 a-d)**. She was tachypneic at rest with an oxygen saturation of 95% in room air. Investigations showed blood urea 35 mg/dL, serum creatinine 0.7 mg/dL, serum sodium 136 mEq/L, serum potassium 3.9 mEq/L, urine albumin 3+, urine protein/creatinine ratio 6.9, 24-hour urine protein 4.95 g/day, serum albumin 3 g/dL, serum cholesterol 397 mg/dL, and respiratory alkalosis with normal anion gap metabolic acidosis on blood gas. Ultrasound abdomen revealed contracted right kidney (6.3 cm), a cortical cyst (1.5 cm) over the left kidney (8.6 cm) and grade 2 renal parenchymal disease indicative of bilateral hypodysplastic kidneys (an anomaly in the CAKUT spectrum). A micturating cystourethrogram was normal, ruling out vesicourethral reflux. Considering her clinical scenario, the renal biopsy was deferred. High resolution computed tomography of the chest showed features of interstitial lung disease **(*Web Fig.* 1e)**. Skin biopsy done at the age of 4 years had revealed blisters within the lamina lucida, and she currently had atrophic scars. A provisional diagnosis of ILNEB syndrome was made. Next generation sequencing of an EDTA sample of her peripheral blood revealed a homozygous 3' splice site mutation (c.1825-1G>A) in intron 13 of the *ITGA3* gene which resulted in frameshift and formation of a premature termination codon in exon 14, p.(Val609SerfsTer31) **(*Web Fig.* 1f)**. She was advised for regular follow-up but succumbed to respiratory complications after 6 months.

Nine patients have been reported earlier [1-6], 7 among them had homozygous ITGA3 mutations. Six among these 7 cases presented with symptoms at birth and expired before two year of age [1-4]. The seventh patient presented in his late teens with isolated involvement of skin and mucosa without any systemic symptoms. The authors suggest that the low level of mutant ITGA3 expression might explain the lack of systemic involvement in this patient. Two other patients were siblings with compound heterozygous ITGA3 mutations without renal involvement and were viable [5]. The case presented here has a homozygous ITGA3 mutation that that is predicted to result in a truncated or dysfunctional ITGA3 protein. Residual activity of the truncated ITGA3 protein could explain the survival of this patient past infancy. Unlike other reported cases of ILNEB where respiratory involvement manifested within few days of life, the present case manifested with dermatological symptoms earlier and later developed renal and respiratory symptoms.

Presence of skin and renal complaints in a patient should make us suspect pulmonary involvement. This will allow an early diagnosis of the disease in order to initiate appropriate management of the complications and genetic counselling.

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REFERENCES

1. Has C, Sparta G, Kiritsi D, Weibel L, Moeller A, Vega-Warner V, *et al*. Integrin alpha3 mutations with kidney, lung, and skin disease. N Engl J Med. 2012;366:1508-14.
2. Nicolaou N, Margadant C, Kevelam SH, Lilien MR, Oosterveld MJ, Kreft M, *et al*. Gain of glycosylation in integrin alpha3 causes lung disease and nephrotic syndrome. J Clin Invest. 2012;122:4375-87.
3. Yalcin EG, He Y, Orhan D, Pazzagli C, Emiralioglu N, Has C. Crucial role of posttranslational 79 modifications of integrin alpha3 in interstitial lung disease and nephrotic syndrome. Hum Mol Genet. 2015;24:3679-88.
4. He Y, Balasubramanian M, Humphreys N, Waruiru C, Brauner M, Kohlhase J, *et al*. Intronic ITGA3 mutation impacts splicing regulation and causes interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa. J Invest Dermatol. 2016;136:1056-9.
5. Colombo EA, Spaccini L, Volpi L, Negri G, Cittaro D, Lazarevic D, *et al*. Viable phenotype of ILNEB syndrome without nephrotic impairment in siblings heterozygous for unreported integrin alpha3 86 mutations. Orphanet J Rare Dis. 2016;11:136.
6. Cohen-Barak E, Danial-Farran N, Khayat M, Chervinsky E, Nevet JM, Ziv M, *et al*. A nonjunctional, nonsyndromic case of junctional epidermolysis bullosa with renal and respiratory involvement. JAMA Dermatol. 2019; 155:498-500.

Successful Right Atrium-Pulmonary Artery ECMO in an Infant With Severe Necrotizing Pneumonia and Bilateral Bronchopleural Fistula

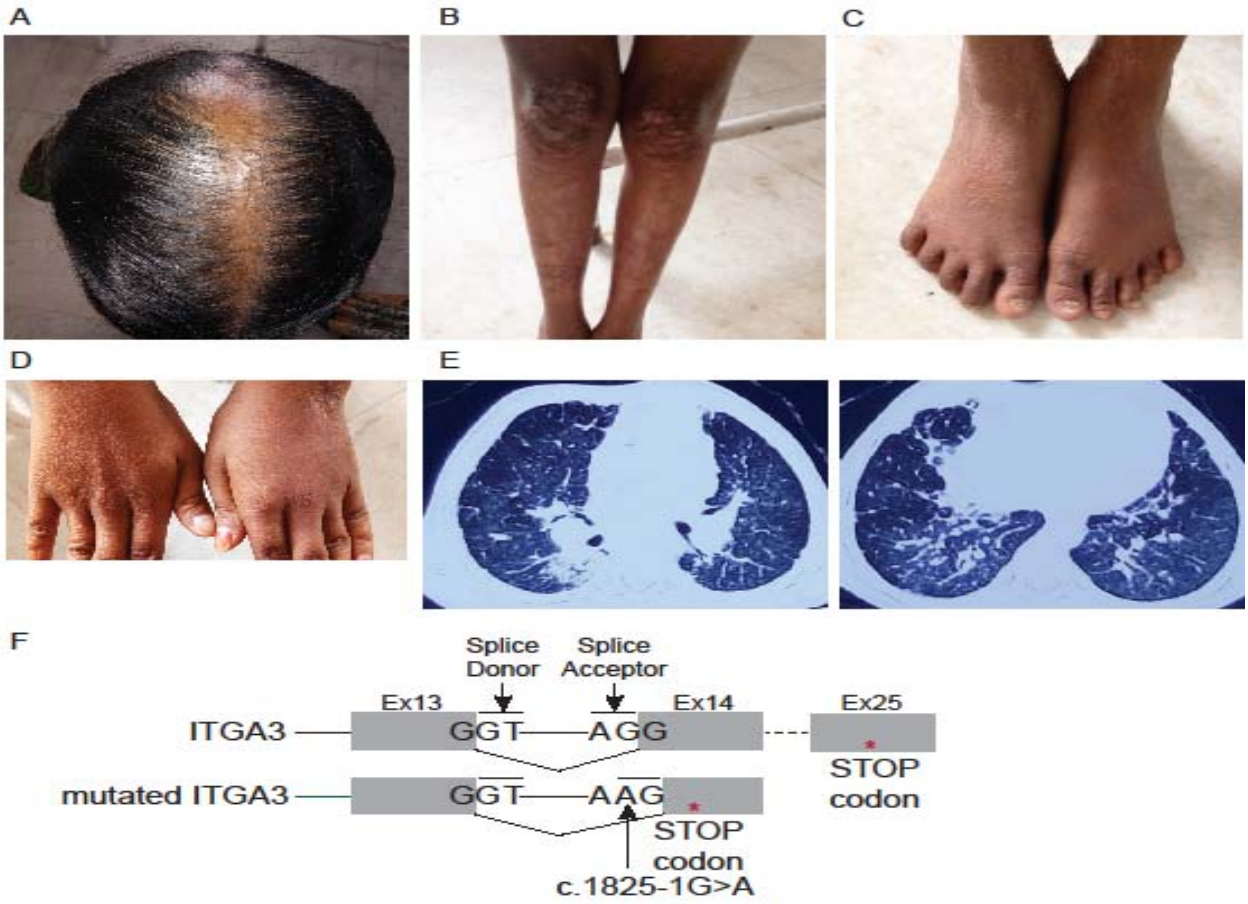
We report an infant with necrotizing pnuemonia and bilateral broncho pleural fistula, who failed on conventional and high frequency ventilation and was managed successfully on Veno-venous Extra Corporeal Membrane Oxygenator (V-V ECMO) with a unique configuration for 12 days, and weaned off successfully.

Keywords: Severe Pneumonia, Management, Ventilation.

Necrotizing pneumonia is a rare form of complicated pneumonia, which often develops secondary to organisms like *Staphylococcus aureus* and *Streptococcus pnuemoniae*. It is often difficult to manage, and occasionally develops complications like pneumothorax and broncho-pleural fistula (BPF).

An 11-month-old infant, weighing 9 kg, was referred to us for respiratory distress and fever of 3 days. He had no significant past medical history, was immunized for age and thriving well. Clinical examination revealed features of bronchopneumonia. He was started on high flow nasal cannula (HFNC) oxygen and broad-spectrum antibiotics. Investigations revealed pancytopenia with elevated inflammatory markers. His clinical condition worsened on day 3 of admission with increasing oxygen requirement (FiO_2 60%) and High flow nasal cannula (HFNC) support (flow 20L/min). He was electively ventilated and put on pressure regulated volume control (PRVC) mode of ventilation. Ventilation protocol was set to targets as suggested in Pediatric acute respiratory syndrome (pARDS) guidelines. The PaO_2 /FiO_2 (PF ratio) was less than 150 with PCO_2 <70mm Hg and PH >7.2. Initial blood culture grew *Psuedomonas* and injectable meropenam treatment was started. Prone ventilation was tried but had to be discontinued after two hours as saturations worsened. *X*-ray showed multiple large pneumatoceles**.** On day 7, he developed pneumothorax on right side; draining intercostal tube showed continuous bubbling suggesting a bronchopleural fistula (BPF). Ventilation was continued with high frequency oscillatory ventilation (HFOV). Maximum settings on HFOV were FiO_2 of 60%, mean airway pressure (MAP) of 16 cm H2O and amplitude (delta P) of 45. Child did show some improvement with improving blood gases and was maintained on neuro-paralysis. After one week on HFOV, *X*-ray showed regressing pneumatoceles with PF ratio improving to >200. $PaCO_2$ was consistently less than 60 mm Hg and PH>7.3 with HFOV settings of FiO_2 40%, MAP of 14 cm H2O and amplitude of 40. On day 13, he was weaned off paralysis and changed back to PRVC mode, but developed tension pneumothorax on left side on the next day.

Considering the child to have refractory Acute respiratory distress syndrome (ARDS) with bilateral air leak, Veno-Venous ECMO was initiated on day 15 of hospital admission. Patient's jugular vein on ultrasound was found to be small hence we decided for central open ECMO. Child was initially put on Veno–venous configuration with inflow and outflow cannulas in right atrium, but had to be re-configured in view of poor flow and re-circulation. Right atrium was cannulated with 22F cannula and pulmonary artery with 14 F cannula, and flow of 900-1000 mL/min was obtained. He was maintained on ECMO for 12 days. On day 12 of ECMO, prior to weaning a bronchoscopic clearance and lavage was taken, which showed carbapenam resistant *Acinetobacter* on culture. Antibiotics were accordingly changed to colistin and tigecycline. Post-ECMO weaning on ventilator, child did



Web Fig. 1 *(a) Scarring alopecia of the scalp; (b) Healed atrophic scars over both shins and knees; (c) Toe nail dystrophy; (d) Clubbing of digits due to interstitial lung disease; (e) High resolution CT of the chest with features of interstitial lung disease; (f) the homozygous ITGA3 mutation c. 1825-1G>A leads to frameshift with formation of a premature termination codon in exon 14, P. (Val609SerfsTer31).*