ABCA3 Deficiency in a Newborn with Respiratory Failure

Deficiencia de ABCA3 en un recién nacido con insuficiencia respiratoria

Dear Editor,

Congenital surfactant deficiencies are rare conditions, including mutation in the surfactant protein B (SP-B), surfactant protein C (SP-C) and ABCA3 (ATP-binding cassette member A3) genes. They may present with respiratory failure and pulmonary hypertension (PH) in the newborn. Long-term outcomes are different according to the mutations.

We present an infrequent case, diagnosed in a tertiary hospital, who has survived.

A term female Arabian infant was born via spontaneous vaginal delivery. Mother and father were consanguineous. Immediately after birth, the infant developed respiratory distress and was initially managed with continuous positive airway pressure.

Her physical examination was notable for bilateral coarse breath sounds and generalized thoracic retractions. Chest radiograph demonstrated diffuse bilateral granular opacities. An echocardiogram revealed no evidence of anatomic heart disease with suprasystemic levels of pulmonary artery pressure. Over the next days, her gas exchange worsened, needing intubation and mechanical ventilation. She developed progressive hypoxic respiratory failure that needed high frequency oscillatory ventilation, and nitric oxide administration.

The infant was treated with antibiotics but infectious causes for PH were ruled out with negative blood cultures. Chest computer tomography (Fig. 1) at 15 days of life showed bilateral granular opacities and ground-glass opacification; two doses of surfactant were administered without improvement. Bronchoscopic bronchoalveolar lavage detected PAS positive material. With this information, a lung biopsy trough video thoracoscopy was performed. There were marked alveolar epithelial hyperplasia and mild widening of alveolar walls and the suspicion of a genetic disorder of surfactant dysfunction was considered. She still needed mechanical ventilation and take away a treatment with monthly high intravenous doses of methylprednisolone in association with oral daily hydroxychloroquine and every other day azithromycin. Genetic testing showed a nonsense mutation in ABCA3 gene, c.4681C>T or p.R1561X. This mutation was present on both maternal and paternal alleles.

At 7 months of age the infant was transferred to a pediatric lung transplant unit where she underwent bilateral lung transplantation at 10 months of age. Currently she is 2 years old needing home mechanical ventilation support because of tracheal and right main bronchus malacia.

Interstitial lung diseases (ILD) are a heterogeneous group of pathological processes that affect pulmonary parenchyma and, in most cases, lead to an impairment of gas transfer and reduction of the lung capacity. There are no reliable estimates, but prevalence is likely <1 per 100 000.[1]

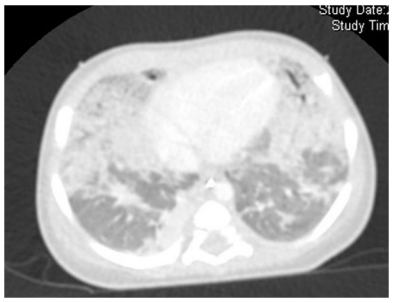

Fig. 1. CT with bilateral granular opacities and ground-glass opacification.

The definition requires at least three of the four following criteria in the absence of other know lung disorders: (1) respiratory symptoms (cough, rapid and/or difficult breathing, or exercise intolerance), (2) signs (resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse abnormalities on chest X-ray or CT scan. Thus, establishing 3 of 4 criteria is a sensitivity method for recognizing patients that could benefit from and ILD evaluation.[2]

The earliest presentation of ILD is shortly after birth, with unexplained respiratory distress in a term neonate.

An organized classification scheme for ILD in children less was published by the chILD Research Network[3–5] (Table 1).

Given the non-specific presentation of ILD, difficulty is frequently experienced in discerning ILD. Excluding these conditions prior to proceeding to more invasive test is important[1,2,6]:

- **Infection screen**.
- An **echocardiography** to rule out structural cardiovascular disease and pulmonary hypertension.
- Baseline **chest X-ray**.
- Thin-**section CT** scanning. Ground glass opacification and air trapping are classical features detected.
- **Flexible bronchoscopy with BAL** to exclude infection or airway abnormalities.
- **Genetic testing**. Surfactant protein mutations produce recognizable clinical phenotypes of varying severity.
- **Lung biopsy** is the gold standard.

The gene for ABCA3 is expressed in alveolar type II cells, and the protein is localized to lamellar bodies. ABCA3 mutations have been associated with lethal neonatal respiratory distress and surfactant metabolism dysfunction. Outcomes in patients with ABCA3 mutations are variable, ranging from severe irreversible respiratory failure in early infancy to chronic static or progressive ILD.[7,8]

There have been no controlled trials of therapeutic interventions in ILD syndrome. Case reports of improvement have been recorded with use of glucocorticoids, hydroxychloroquine, azathioprine, bronchodilators, mycophenolate, and other immune modulators.[9,10] Lung transplantation is an option in end-stage lung disease.[11]

Table 1
Classification for ILD in Children.

Diffuse developmental disorders	Acinar dysplasia, congenital alveolar dysplasia, alveolar-capillary dysplasia
Growth abnormalities	Pulmonary hypoplasia, structural pulmonary changes with chromosomal abnormalities
Specific conditions of undefined etiology	Pulmonary interstitial glycogenosis, neuroendocrine cell hyperplasia of infancy
Surfactant dysfunction mutations	SPFTB, SPFTC, ABCA3 genetic mutations
Disorders of the normal host	Infectious processes, environmental agents, aspiration syndromes, eosinophilic pneumonia
Disorders related to systemic disease processes	Immune-related disorders, storage disease, Langerhans cell histiocytosis
Disorders masquerading as interstitial disease	Arterial hypertensive vasculopathy, congestive vasculopathy, lymphatic disorders

The North American Children study[12] found a mortality rate of 30%, with 50% of patients experiencing on-going morbidity. It has become clear that some ILD entities are associated with very high mortality, whereas others have a favorable outcome.

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Tuberculosis y poliangitis microscópica. Una asociación muy poco frecuente

Tuberculosis and Microscopic Polyangiitis. A Rare Combination

Estimado Director:

La tuberculosis (TB) es una de las causas más frecuentes de morbimortalidad en el mundo debida a una enfermedad infecciosa, con una incidencia en nuestra región, en el año 2015, de 21,3 casos/100.000 habitantes[1].

Las vasculitis son un grupo heterogéneo de enfermedades que se caracterizan por inflamación y destrucción de la pared de los vasos sanguíneos[2]. La mayoría suelen ser primarias, pero también pueden ser secundarias a otras enfermedades, entre ellas las infecciosas[3]. En ocasiones, diferenciar entre TB y vasculitis puede ser difícil porque comparten características similares, y en otras, ambas pueden coexistir en un mismo paciente[4]. Las definiciones de las vasculitis y sus diferencias están bien establecidas[5]. Presentamos el caso de un enfermo que comenzó simultáneamente con TB y poliangitis microscópica (PAM).

Se trata de un varón de 68 años con antecedentes de TB, que acudió a Urgencias por fiebre, esputos hemoptoicos, astenia, pérdida de peso y disnea de un mes de evolución. Presentaba una temperatura de 38,4 °C, sin otros hallazgos relevantes. La analítica sanguínea era normal y en la radiografía de tórax se observaban lesiones cicatriciales en el lóbulo superior derecho con una lesión parenquimatosa de aspecto sólido y espiculada. La tomografía computarizada de tórax no demostró alteraciones a nivel de campos medios e inferiores (fig. 1A). No se observó afectación de las vías respiratorias altas. La reacción en cadena de la polimerasa fue positiva para *Mycobacterium tuberculosis* en el aspirado bronquial y el lavado broncoalveolar. La punción con aguja gruesa de la lesión espiculada identificó una inflamación granulomatosa necrosante con células gigantes multinucleadas tipo Langhans (fig. 1B), con tinción de Ziehl-Neelsen y reacción en cadena de la polimerasa para *Mycobacterium tuberculosis* positivas. De forma súbita, presentó hemoptisis con anemia (hemoglobina 6,8 g/dL, hematocrito 20,8%), fallo renal agudo (urea 123 mg/dL, creatinina 8,3 mg/dL), oligoanuria e hipertransaminasemia (valores 5 veces por encima del límite superior normal). El paciente necesitó intubación, ventilación mecánica y hemodiálisis. El tratamiento antituberculoso se inició con etambutol, levofloxacino y estreptomicina debido a las insuficiencias hepática y renal. En la tomografía computarizada de tórax presentaba un aumento difuso de la radiodensidad pulmonar, con predominio de vidrio deslustrado y áreas consolidativas de distribución peribroncovascular con moderado derrame pleural izquierdo loculado, con un componente cisural, que se interpretó como una hemorragia alveolar difusa (fig. 1C). La biopsia renal demostró vasculitis con necrosis fibrinoide de arterias de pequeño calibre, asociada a glomerulonefritis necrosante focal y segmentaria con ausencia de depósitos de inmunoglobulinas, complemento y cadenas ligeras, indicativo de PAM (fig. 1 D y E). El líquido pleural fue un exudado linfocítico; ADA 45 U/L, sin otras alteraciones relevantes. Se detectaron anticuerpos citoplásmicos antineutrófilo (ANCA) (dilución 1/320; patrón p-ANCA) con anticuerpos antimieloperoxidasa > 300 UI/mL. Los anticuerpos antimembrana basal glomerular fueron negativos. Se administraron corticosteroides (3 bolos iniciales de metilprednisolona 500 mg/día, con pauta descendente hasta llegar a 15 mg/día de prednisona), plasmaféresis (7 sesiones), rituximab (una dosis semanal de 700 mg durante 4 semanas) y posteriormente se pudieron reintroducir la rifampicina y la isoniacida. La evolución fue favorable, aunque de forma lenta, con estabilidad clínica desde el punto de vista respiratorio y mejoría radiológica (fig. 1F).

La asociación entre TB y vasculitis está descrita, pero generalmente siempre relacionada con una granulomatosis con poliangitis[4,6,7]. Hasta donde sabemos, este es el segundo caso conocido en el que se asocian TB y PAM[7]. Ambos diagnósticos parecen confirmados: reacción en cadena de la polimerasa positiva en 2 muestras distintas en el caso de la TB, inflamación granulomatosa con necrosis y células gigantes multinucleadas en tejido