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Case Report

Respiratory insufficiency in an infant with osteogenesis imperfecta

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ABSTRACT

Osteogenesis imperfecta (OI) is a rare presentation in the pediatric population. Whilst orthopedic manifestations are well-publicised, the multiple respiratory complications and mechanisms of respiratory failure in more severe cases are less well described. We report the clinical, radiological and histopathological details of the case of an infant with genetically-confirmed OI (Type 2) and associated respiratory insufficiency, as well as summarise the relevant existing literature. This case highlights the importance of the recognition of clinical challenges associated with the management of respiratory complications in a patient with OI.

1. Introduction

Osteogenesis imperfecta (OI), also known as "brittle bone disease", is a genetically and phenotypically heterogenous group of inherited bone dysplasias [1]. OI is most often caused by alterations in Type 1 collagen with an estimated incidence of approximately 1 in 10,000 to 1 in 20,000 [1]. OI can be inherited as a dominant, recessive, or X-linked disorder, with the autosomal dominant mutation occurring at COL1A1/2 in more than 80 % of the patients [2].

There are five clinical forms of OI identified in the revised Nosology and Classification of Genetic Skeletal Disorders: non-deforming with persistently blue sclera (Type 1), perinatal lethal (Type 2), progressively deforming (Type 3), moderate (Type 4), and with calcification of the interosseous membranes and/or hypertrophic callus (Type 5) [3]. In addition, the Online Mendelian Inheritance in Man (OMIM) is a recent classification system which describes the causative genes, mode of inheritance, and clinical phenotypes of over 20 types of OI [4].

While OI is usually associated with fractures, as Type 1 collagen is expressed in all connective tissues, there is multiorgan involvement as evidenced by the associated features of dentinogenesis imperfecta, blue sclerae, hearing impairment, skin laxity, and cardiorespiratory issues [1]. Respiratory disease was found to be a significant contributor to mortality in the patients with OI with a sub-hazard ratio of 3.1 as compared to the reference population [5].

Even with the existing classification systems, prognostication of individual outcomes can be difficult due to limited guiding evidence. Here we report the case of an infant with a genetic diagnosis of OI and discuss the relevant associated pulmonary complications and patient outcome.

2. Case presentation

A male infant was born via elective caesarean section at a peripheral hospital at 37 weeks gestation with a birth weight of 3210 g. The infant was in the breech position and antenatal scans revealed shortened long bones and multiple fractures including those of the femur and ribs, suggestive of skeletal dysplasia. Antenatal microarray analysis (Affymetrix CytoScan 750K array) was unremarkable. At birth, the patient required intermittent positive pressure ventilation (IPPV) for 4 minutes followed by continuous positive airway

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pressure (CPAP) at 5cmH20 once spontaneous respirations were established. The APGAR scores were 5 (1 minute), 9 (5 minutes) and 9 (10 minutes). The infant was then admitted to the Neonatal Intensive Care Unit.

A skeletal survey conducted post birth detected multiple fractures at the bilateral proximal femurs, left clavicle, right ulna and radius, left fibula, and multiple rib fractures of varying ages (Fig. 1). These findings were concerning for OI and therefore genetic testing was performed. Other investigations including the parathyroid hormone level and urine metabolic panel were unremarkable.

The infant was tachypneic (100 breaths per minute) with increased respiratory effort since birth. On Day 1 (D1), respiratory support was changed from CPAP to high flow nasal prongs (HFNP) at 3L/kg with a fraction of inspired oxygen (Fi02) of 0.34. On D9, an echocardiogram was performed which revealed a small patent foramen ovale and moderately increased pulmonary pressures (estimated right ventricle systolic pressure [RVSP] of 44 mmHg). On a repeat echocardiogram on D26, mild left ventricular hypertrophy, mild tricuspid regurgitation and estimated RVSP of 43 mmHg was noted.

On D45, the patient had a respiratory deterioration in the setting of suspected sepsis with bilateral air space changes present on a chest X-ray (Fig. 2). Intravenous (IV) flucloxacillin, gentamicin and cefotaxime were commenced. The hypoxic respiratory failure worsened on D47 resulting in intubation, ventilation and retrieval to a tertiary Pediatric Intensive Care Unit. After six days (D53), the child was extubated to HFNP support. The tracheal aspirate culture was positive for *Klebsiella Pneumoniae*. Hence, treatment with seven days of IV cefotaxime and a further week of oral amoxicillin-clavulanic acid was completed.

In addition, the infant was unsettled with persistent tachycardia and hypertension since birth, thought to be secondary to the pain from multiple fractures. This was managed with regular oral analgesia including opioids, intermittent intravenous morphine infusion and splinting of fractures. The child was nursed with minimal handling, given the risk of further fractures. Bisphosphonate therapy was also discussed as a measure to improve pain, which was declined by the family due to the risk of a consequential serious acute systemic inflammatory response [6].

Genetic testing subsequently returned a finding of a heterozygous pathogenic mutation of COL1A2; c.1937G > T (Fulgent, Osteogenesis imperfecta and decreased bone density genetic panel) which is associated with OI (phenotypes 2–4), contributing to challenges surrounding prognostication. There was no family history of bone disorders or OI, and the patient was the first child born to non-consanguineous parents.

The child remained on HFNP 3L/kg with persistent tachypnea and hypoxemia with multiple unsuccessful trials of weaning the respiratory support. CPAP was not re-administered, given the potential for further discomfort and facial trauma. As the infant was re-

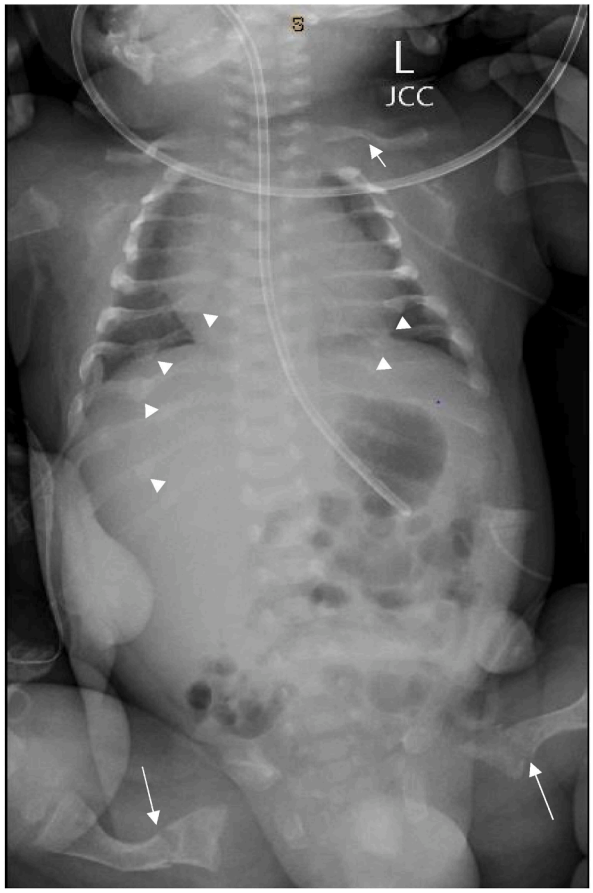

Fig. 1. Part of a skeletal survey depicting multiple fractures of the ribs (white arrowheads), left clavicle (short arrow), proximal right and left femur (long arrows).

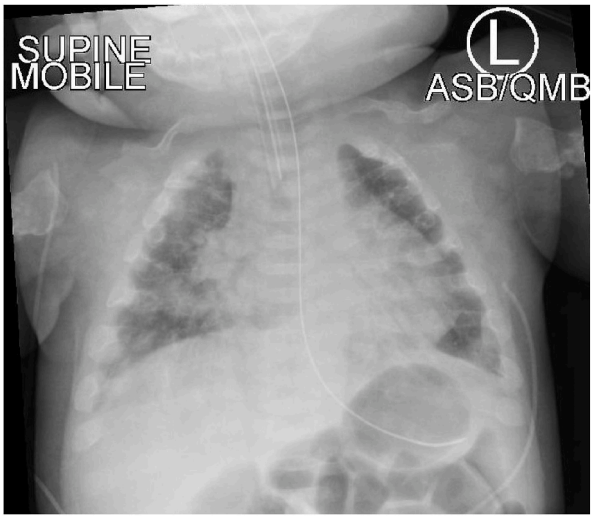

Fig. 2. Chest X-ray revealing bilateral air space changes with multiple rib fractures and markedly reduced bone density.

quiring persistent respiratory support without plausible prospect for improvement, and experiencing significant discomfort despite limited handling, the treating teams, parents, and palliative care team supported an approach focussed on comfort rather than life prolongation. Pain management was greatly improved with escalating multimodal analgesia and the infant passed away 75 days after birth.

A postmortem examination of the right upper and middle lung lobes was performed via a right sided thoracotomy. The lung tissue was fixed in formalin prior to sectioning. On histological assessment, large alveoli were seen, with a radial alveolar count of approximately three, consistent with pulmonary hypoplasia (Fig. 3). Additionally, fibromuscular hyperplasia with thickening of intraparenchymal arteriolar walls was noted (Fig. 4), consistent with pulmonary hypertension. There were no features of inflammation, acute infection or pulmonary fibrosis seen. Informed consent was obtained from both parents for the publishing of this case report.

3. Discussion

In patients with OI, the risk and severity of respiratory complications appears closely associated with the severity of OI. At birth, infants with OI Type 3 were 3.9 times more likely to have respiratory concerns as compared to the children with OI Types 1 and 4 [7]. In another study, respiratory tract infection was identified as the most frequent cause of death in OI, with a mean age at death of 6.2 years in the severe phenotype (Type 3) and a greater age of 63.5 years in the milder phenotypes (Types 1 and 4) [8]. In addition, individuals with OI Type 3 have been found to have significantly reduced forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) compared to those with OI Types 1 and 4 [9].

Importantly, there are multiple different pulmonary complications that can arise in OI independently or in conjunction with (and compounding) one another. These include abnormalities of the thoracic cage, diaphragm, and lung parenchyma, as well as respiratory tract infections and pulmonary hypertension.

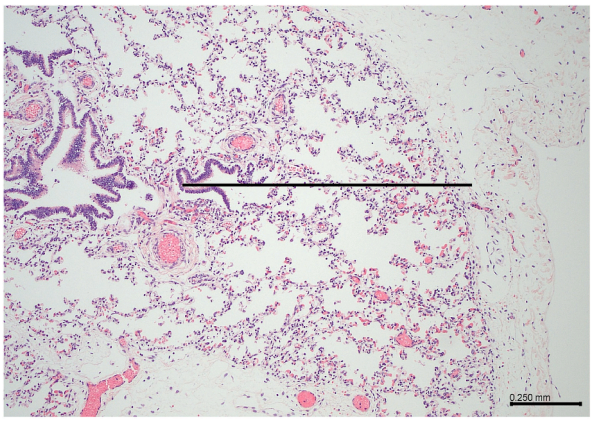

Fig. 3. Lung histology at high magnification (x400) depicting pulmonary hypoplasia with decreased radial count between the bronchiole and pleura (black line). Section stained with hematoxylin and eosin.

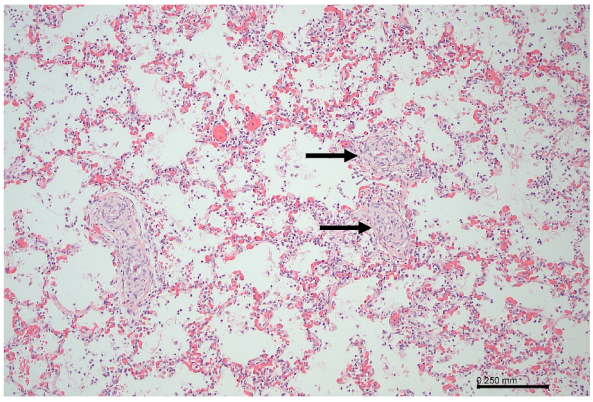

Fig. 4. Lung histology at high magnification (x400) depicting arterioles with fibromuscular hyperplasia (arrows). Section stained with hematoxylin and eosin.

Restrictive lung disease is a key manifestation of OI-associated pulmonary disease and is contributed by altered thoracic wall architecture. Patients with OI may present with rib fractures, kyphoscoliosis, vertebral collapse and restricted movement of the diaphragm from upward compression of abdominal contents due to short stature [10,11]. Assessment of chest wall geometry with optoelectronic plethysmography revealed altered respiratory muscle coordination, thoraco-abdominal asynchrony, inefficient ventilation patterns and associated pulmonary function impairment, more prominently noted in OI Type 3 as compared to Type 4 [10].

Respiratory compromise in OI does not necessarily arise solely from the bony deformities of the thoracic cage however, as intrinsic defects of the lung parenchyma have been noted [12]. A previous case report detailed the lung histology of a term infant with perinatal lethal Type 2 OI. The study showed a marked decrease in the alveolar number, decrease in the quantity of parenchyma in relation to hilar structures and hypercellular alveolar walls, consistent with immature acinar development [13]. Other studies, including those on mouse models have also been performed and some similarities to our patient's findings were observed. Studies by Dimori et al. revealed abnormal lung histology with alveolar simplification and reduced alveolar surface as well as emphysema-like changes [14]. Additionally, Col1a1$^{Jrt/+}$ mice with severe dominant OI have been shown to exhibit a reduction in diaphragmatic thickness and fibre size, associated with decreased muscle mass and intrinsic contractile weakness [15].

Respiratory tract infections also occur more frequently in those with OI, and can be acute and/or chronic in nature [12]. These can lead to bronchiectasis, decline in lung function and impairment of gas exchange [12]. Furthermore, cardiac abnormalities such as aortic root dilatation, increased septal and posterior left ventricular wall thickness [16] and associated pulmonary hypertension in the setting of pulmonary hypoplasia can also contribute to overall cardio-pulmonary insufficiency [17]. Over time, further cardiac complications may occur including valvular insufficiency [16] and chronic pulmonary insufficiency progressing to cor pulmonale [17].

In the setting of acute respiratory failure, in-hospital respiratory support including both non-invasive and invasive ventilation can be considered. Additionally, the use of at-home non-invasive ventilation for children with OI has been previously reported [18]. Whilst there is a scarcity of literature regarding the use of tracheostomy and long-term invasive respiratory support for children with OI, a single review article suggests that this may be required and warranted in extreme cases [19]. This must be carefully evaluated in collaboration with the patient's family and the multidisciplinary team, to ensure the best interests of the child are prioritized [20].

Overall, the management of OI is primarily supportive with the main goals of improving bone strength, decreasing fracture risk, reducing pain, and enhancing functional independence [21]. Patients usually require a multidisciplinary team approach with the involvement of a wide range of specialists and experienced allied health staff to optimise their care. Bisphosphonates are presently the main therapeutic agent available to improve bone mass and architecture as well as to reduce fracture risk, while denosumab, teriparatide, sclerostin antibody, TFTβ inhibitory antibody and cell therapy are undergoing clinical trials [21,22]. However, bisphosphonate therapy is not without risk [6]. Additionally, pain is a well-recognised burden of OI and it best managed in infants with a comprehensive, multimodal approach [23].

4. Conclusion

OI is a rare and complex condition with multisystem involvement. Our patient had severe Type 2 OI, with subsequent demise from respiratory insufficiency secondary to pulmonary hypoplasia and pulmonary hypertension. Lung histology revealed a significant intrinsic parenchymal abnormality, highlighting the fact that the pulmonary defects associated with OI are congenital in nature and not limited to those arising from bony abnormalities and respiratory tract infections. While management and prognostication remain challenging, early involvement of an experienced multidisciplinary team to optimise care and facilitate discussions and appropriate decision-making plays an integral role in the management of patients with osteogenesis imperfecta.

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CRediT authorship contribution statement

Adeline Yi Ling Lim: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ajay Kevat:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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