# Case Report

# Perinatal Lethal Osteogenesis Imperfecta in a Thai Newborn: The Autopsy and Histopathogical Findings

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*Osteogenesis imperfecta (OI) is an inherited disorder of type I collagen synthesis with an estimate incidence of 1 in 100,000 live births. Among all types, OI type II is the most severe type with perinatal death. The authors describes a male neonate with characteristic features of osteogenesis imperfect type II, including short crumpling limbs, beaded ribs, poorly bony ossification and blue sclera. Autopsy with histological study revealed not only multiple fractures, but pulmonary hypoplasia and intracerebral hemorrhages were also present. Both are the leading causes of death in the lethal type OI patients.*

***Keywords:*** *Osteogenesis imperfect, Fracture, Intracerebral hemorrhage*

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Osteogenesis imperfecta (OI) is a group of hereditary disorders of increased bone fragility, an osteopenia characterized by fractures with minimal or absent trauma and other connective tissue manifestations[1-3]. According to the 2010 revision of International Nosology and Classification, OI was classified into various types namely I, IIA, IIB, III, IV, V, VI, VII, VIII and IX based on clinical features, severity of the disease and molecular findings[4,5]. Here the authors present an autopsy study of a rare case of perinatal lethal OI which is one of the severe forms of this entity and to the authors best knowledge has not been reported in Thailand.

## Case Report

A preterm newly born male infant was the first child of non-consanguineous parents. The parents were 28 years old and phenotypic normal. His primigravida mother had not received prenatal care and she came to the hospital because of labor pain. He was born at 34 weeks' gestation by cesarean section due to fetal distress. The Apgar scores were 3 and 7 at 1 and 5 minutes, respectively. He developed respiratory distress at birth that required endotracheal intubation and ventilator support. He was admitted to the neonatal intensive care unit.

On physical examination, he was a disproportionately grown and short stature infant, his weight was 1,515 g (-2 SD), length was 34 cm (< -2 SD) and head circumference was 28 cm (-2 SD). He had dysmorphic features including soft calvarium, shallow orbits and blue sclera. Deformed and short limbs, small thorax, multiple ribs and long bones fractures with platyspondyly of vertebrae were noted in the radiography (Fig. 1B).

He had tachypnea and retraction with no improvement from ventilator support. His vital signs were in normal range except for his respiratory rate is 70-100/min, until the sixth day after birth, he died of respiratory failure. An autopsy was performed.

## Autopsy findings

The body was that of a male newborn whose body weight was 2,500 grams. The crown-heel length was 34 cm. Both upper and lower extremities appeared short and depressed. Right indirect inguinal hernia was present. The head was soft corresponded to poorly ossified calvarium by the radiograph (Fig. 1A, 1B). Both sclerae were deep grey-blue. The so-called "beaded ribs", crumpling femurs, marked long bone deformity and platyspondyly spine (Fig. 1A, 1B) were noted.

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Histological sections from the rib (Fig. 2B) revealed irregularity of osteocartilaginous junction with paucity of bone-trabeculae of primary and secondary spongiosa. The cortex was markedly thin and multi-foci of disruption due to previous fracture were noted. There was an inguinal hernia in the right groin containing part of duodenum, ileum and ascending colon but no gangrene or peritonitis was present. The heart was normal in size and shape. A ductus arteriosus measuring 0.2 cm in diameter was observed connecting the aorta and pulmonary trunk. Bilateral lungs showed immaturity and "pulmonary hypoplasia" (A ratio between lungs and body weight was less than 0.012 for fetus with gestational age of more than 28 week). The histopathology of lungs showed hyaline membrane, pulmonary congestion and edema (Fig. 3A, 3B). The calvariums were soft and appeared semi-translucent which corresponded with the paucity of bone formations in the process of membranous ossification in the skull by histological examination. Dark-red areas on bilateral temporal represented focal areas of hemorrhages in the calvarium (Fig. 4A, B). Diffuse subarachnoid and intraventricular hemorrhage were noted in the right temporo-parietal area (Fig. 5A).

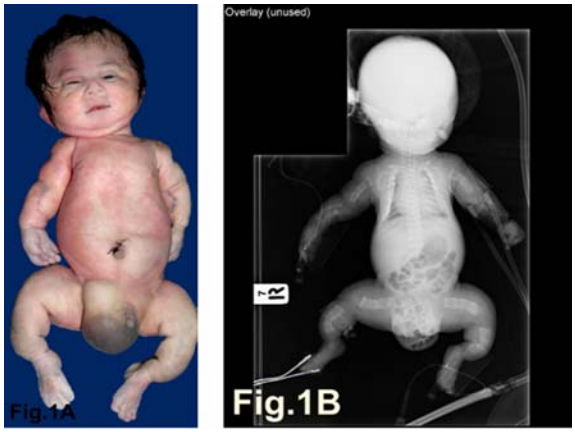


**Fig. 1** Anatomical findings. A) Whole body showing crumpled extremities (suggesting multiple fractures) and inguinal hernia on the right side B) Babygram showing generalized osteopenia and multiple fractures

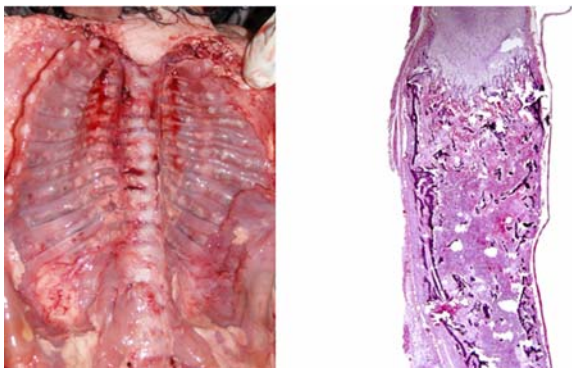

**Fig. 2** A) Gross examination when viewing from the intra-thoracic cavity showing beaded ribs and platyspondyly spine B) Histology of the rib showing irregular osteocartilaginous junction with paucity and thin trabeculae of the primary and secondary spongiosa. The cortical bone showed markedly thin and disrupted periodically, possibly due to previous fracture

## Discussion

The case showed osteopenia and multiple fractures during intrauterine period, bone as shown by

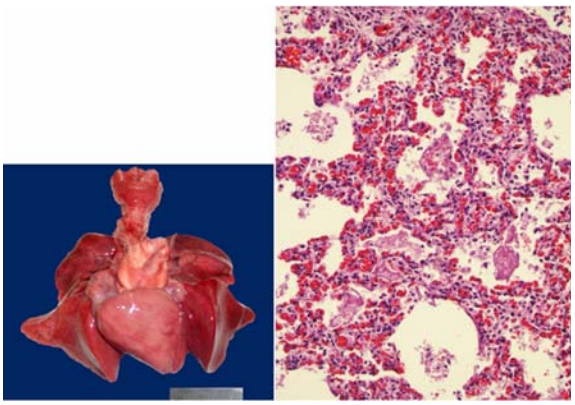

**Fig. 3** Lungs A) showing decrease in size of bilateral lungs B) Histology showing immature lungs with congestion and hyaline membrane, compatible with clinically diffuse alveolar damage and respiratory failure

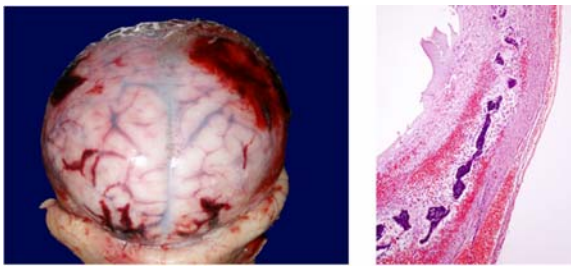

**Fig. 4** Skull A) Semi-translucent calvarium with soft consistency B) Histologically, the cavarium showed disconnected thin islands of bone representing decrease in bone formation in the process of membranous ossification; there were also extensive hemorrhagic areas in the fibrous stroma

x-ray and confirmed by pathologic findings. Blue sclera was also found and fulfilled the criteria for perinatal lethal form of OI as shown in Table 1 and 2.

Previously, osteogenesis imperfecta (OI) was classified into 4 types, type I-IV according to Sillence classification which based on only clinical features and genetic defects regarding production of collagen type I[5]. Nowadays, OI is classified into 9 types based on mode of inherited, clinical findings, histological features and mutated gene regarding not only collagen production but also included the production of some other extracellular substances as summarized in Table 2. The severity increasing from type I < types IV, V, VI, VII < type III < types VIII, IX < type II[2,6]. From clinical consideration per se, perinatal lethal form may be classified as type IIA (MIM 166210), *COL1A1 or COL1A2* mutation, which was found in most cases or types IIB (MIM610854), VIII (MIM 610915) or IX (MIM 259440) of which mutated gene

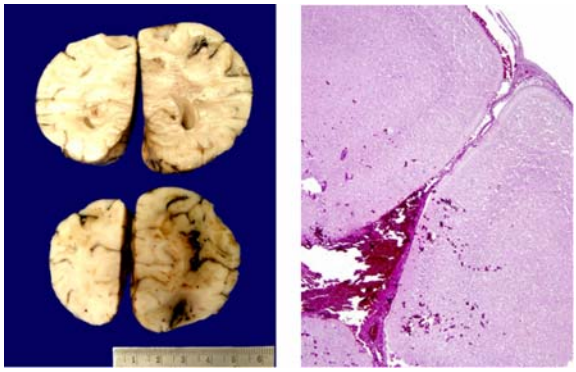

**Fig. 5** Brain A) Showing intraparenchymal and intraventricular hemorrhage of right temporoparietal region B) Histology showing recent hemorrhage in the ventricle and cerebral edema

*CRTAP*, *LEPRE1* or *PPIB* were identified in 5% of cases[7,8].

Perinatal lethal OI or OI type II was also divided into 3 groups based on radiological subclassification; II-A which is characterized by broad ribs with multiple fractures, continuous beaded ribs and severe under-modeling femur, II-B by normal or thin ribs and discontinuous beaded ribs and II-C by varying thickness of ribs, discontinuous beaded ribs and slender twisted long bones[9]. According to Sillence Classification, our case should be classified as OI type IIA because of the findings of short, beaded ribs, crumpled long bone due to multiple fractures and poor bone- remodeling[10-12].

The prevalence of OI is 6-7/100,000. Mild form (type I and IV) is found more than half of cases and incidence of OI type II is 1-2/100,000 but now it may be less due to early prenatal recognition[3]. Perinatal lethal OI can be recognized earliest in 12-13 weeks' gestation by prenatal ultrasound; the accuracy ranged from 34-65%[13-15].

The cause of death in the case should be due to : firstly, pulmonary hypoplasia with respiratory failure that related to multiple intrauterine rib fractures causing limitation of lung expansion[16,17]; secondly, intracerebral hemorrhage which might occur due to birth injury[11] or even spontaneous bleeding by vascular collagen defect in non-lethal types of OI[18,19]. This case was born by caesarean section without evidence of head injury plus the stable blood pressure during admission time, so spontaneous intracerebral hemorrhage was more-likely.

We did not have molecular study for this case due to unavailable facility. However, most of perinatal lethal OI showed mutation of *COL1A1&2* genes and transmitted as autosomal dominant inheritance and approximately 5-9% of cases showed germline

**Table 1.** Skeletal disorders in differential diagnosis with perinatal lethal OI

| Disorders | Bone fragility plus | Cause |
|---|---|---|
| Bruck syndrome (osteogenesis imperfecta with congenital joint contractures) | Joint contractures | Defects in lysyl hydroxylase (crosslink formation), AR inheritance |
| Osteoporosis pseudoglioma syndrome (ocular form of osteogenesis imperfect) | Blindness in infancy | Mutations in lipoprotein receptor-related protein-5 geneAR inheritance |
| Hypophosphatasia, perinatal type | Low bone turnover and low serum alkaline phosphatase | mutation in the gene encoding tissue-non specific alkaline phosphatase (ALPL), AR inheritance |
| Cole-Carpenter syndrome | Craniosynostosis and hydrocephalus | Unknown |

Modified from references[2,3]

**Table 2.** Summarized new classification of OI

| Type | Severity | Clinical features | DI | sclera | Mode of inheritance | Mutated gene |
|---|---|---|---|---|---|---|
| I | Mild | Normal height or slightly short, few to 100 fractures, no bone deformity, wormian skull, codfish vertebrae, progressive hearing loss (50% in adult) | rare | blue | AD | *COL1A1* |
| IIA | Lethal | Multiple ribs and long bone fractures, small beaded ribs, short stature, severe deformity, minimal calvarial mineralization, platyspondyly vertebrae | - | dark blue | AD | *COL1A1* or *COL1A2* |
| IIB | Same as IIA | | | | AR | *CRTAP* |
| III | Severe | Very short stature, triangular face, severe scoliosis, marked bone deformity, flared metaphyses, severe osteoporosis | + | Gray/ blue | AD, rare AR | *COL1A1* or *COL1A2* |
| IV | Moderate | Moderately short, mild to moderate scoliosis, thin ribs, protrusia acetabuli | +/- | White/ gray | AD | *COL1A1* or *COL1A2* |
| V | Moderate | Mildly to moderately short, multiple with hypertrophic callus | No | White | AD | Unknown |
| VI | Moderate to severe | Moderately short, Rhizomelic shortening | No | White | Uncertain | Unknown |
| VII | Moderate | Mildly short | No | White | AR | *CRTAP* |
| VIII | Severe to lethal | Severe deformity to perinatal lethal | - | White | AR | *LEPRE1* |
| IX | Severe to lethal | Similar to type II-III | -/+ | Blue/white | AD | *PPIB* |

Modified from references[1-3,6,12]

mosaicism; Only few cases of AR inherited perinatal OI, the recurrent risk is up to 25% in the couples who are both carriers[11,20].

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**Potential conflicts of interest**

None.

**References**

1. van Rooijen N. Applicabilities of some modifications of a double isotope autoradiographic method for separate detection of 3H and 131I or 32P in tissue sections or cell smears. Cell Mol Biol Incl Cyto Enzymol 1977; 22: 347-52.
2. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet 2004; 363: 1377-85.
3. Steiner RD, Pepin MG, Byers PH. Osteogenesis Imperfecta. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [database on the Internet]. Seattle, WA: University of Washington, Seattle; 2005 [cited 2011 Sep 19]: [16 screens]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1295/
4. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A 2011; 155A: 943-68.
5. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979; 16: 101-16.
6. Cabral WA, Chang W, Barnes AM, Weis M, Scott MA, Leikin S, et al. Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. Nat Genet 2007; 39: 359-65.
7. Bodian DL, Chan TF, Poon A, Schwarze U, Yang K, Byers PH, et al. Mutation and polymorphism spectrum in osteogenesis imperfecta type II: implications for genotype-phenotype relationships. Hum Mol Genet 2009; 18: 463-71.
8. Marini JC, Forlino A, Cabral WA, Barnes AM, San

Antonio JD, Milgrom S, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. Hum Mutat 2007; 28: 209-21.
9. Sillence DO, Barlow KK, Garber AP, Hall JG, Rimoin DL. Osteogenesis imperfecta type II delineation of the phenotype with reference to genetic heterogeneity. Am J Med Genet 1984; 17: 407-23.
10. Cheung MS, Glorieux FH. Osteogenesis Imperfecta: update on presentation and management. Rev Endocr Metab Disord 2008; 9: 153-60.
11. Bishop N. Osteogenesis imperfecta. Recent progress in many areas. Clinical Reviews Bone and Mineral Metabolism 2004; 2: 19-36.
12. Van Dijk FS, Pals G, Van Rijn RR, Nikkels PG, Cobben JM. Classification of Osteogenesis Imperfecta revisited. Eur J Med Genet 2010; 53: 1-5.
13. Tongsong T, Wanapirak C, Siriangkul S. Prenatal diagnosis of osteogenesis imperfecta type II. Int J Gynaecol Obstet 1998; 61: 33-8.
14. Konstantinidou AE, Agrogiannis G, Sifakis S, Karantanas A, Harakoglou V, Kaminopetros P, et al. Genetic skeletal disorders of the fetus and infant: pathologic and molecular findings in a series of 41 cases. Birth Defects Res A Clin Mol Teratol 2009; 85: 811-21.
15. Krakow D, Alanay Y, Rimoin LP, Lin V, Wilcox WR, Lachman RS, et al. Evaluation of prenatal-onset osteochondrodysplasias by ultrasonography: a retrospective and prospective analysis. Am J Med Genet A 2008; 146A: 1917-24.
16. Plotkin H. Syndromes with congenital brittle bones. BMC Pediatr 2004; 4: 16.
17. McAllion SJ, Paterson CR. Causes of death in osteogenesis imperfecta. J Clin Pathol 1996; 49: 627-30.
18. Albayram S, Kizilkilic O, Yilmaz H, Tuysuz B, Kocer N, Islak C. Abnormalities in the cerebral arterial system in osteogenesis imperfecta. AJNR Am J Neuroradiol 2003; 24: 748-50.
19. Goddeau RP Jr, Caplan LR, Alhazzani AA. Intraparenchymal hemorrhage in a patient with osteogenesis imperfecta and plasminogen activator inhibitor-1 deficiency. Arch Neurol 2010; 67: 236-8.
20. Pyott SM, Pepin MG, Schwarze U, Yang K, Smith G, Byers PH. Recurrence of perinatal lethal osteogenesis imperfecta in sibships: parsing the risk between parental mosaicism for dominant mutations and autosomal recessive inheritance. Genet Med 2011; 13: 125-30.

## *ลักษณะความผิดปกติทางพยาธิวิทยาจากการตรวจศพ ในทารกไทย 1 ราย ที่เป็นโรคกระดูกเปราะกรรมพันธุ์*

***วันวิสาข์ หิมะคุณ, กิติวรรณ โรจนเนืองนิตย์, ศริยา ประจักษ์ธรรม***

*โรคกระดูกเปราะกรรมพันธุ์ (osteogenesis imperfecta; OI) เป็นโรคทางพันธุกรรม ซึ่งมีสาเหตุจากความผิดปกติของการสังเคราะห์ คอลลาเจน ไทป์ 1 พบอุบัติการณ์ประมาณ 1 ใน 100,000 ของทารกเกิดมีชีพ ผู้ป่วยที่เป็นโรคกระดูกเปราะกรรมพันธุ์ ประเภทที่ 2 จัดเป็นกลุ่มที่มีความรุนแรงของโรคมากที่สุด และมักเสียชีวิตตั้งแต่กำเนิด ผู้นิพนธ์รายงานผู้ป่วยทารกแรกเกิดเพศชาย 1 ราย ซึ่งมีลักษณะทางคลินิกเข้าได้กับโรคกระดูกเปราะกรรมพันธุ์ คือ แขนขาหักงอผิดรูป กระดูกซี่โครงมีรอยหักเชื่อมต่อเนื่องกัน มีการสร้างกระดูกแข็งน้อยกว่าปกติ และมีตาขาวเป็นสีฟ้า การตรวจศพและการตรวจชิ้นเนื้อทางพยาธิวิทยา พบกระดูกหักหลายตำแหน่ง ร่วมกับภาวะปอดเจริญเติบโตน้อย และมีเลือดออกในเนื้อสมอง ซึ่งเป็นสาเหตุหลักของการเสียชีวิตที่พบได้บ่อยที่สุดในผู้ป่วยที่เป็นโรคนี้*