Educational Case

# Educational Case: Osteogenesis imperfecta

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

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## Primary objective

Objective MS2.5: Pathologic fracture: Compare and contrast pathologic versus non-pathologic fractures including the potential for healing.

Competency 2: Organ system pathology; Topic: MS: Musculoskeletal system; Learning goal 2: Non-neoplastic disorders of the musculoskeletal system.

## Secondary objective

Objective GM1.2: Inheritance patterns: Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each pattern.

Competency 1: Disease mechanisms and processes; Topic: GM: Genetic mechanisms; Learning goal 1: Genetic mechanisms of development and functional abnormalities.

## Patient presentation

A two-week-old female infant born at 36 weeks gestational age is brought to her pediatrician by her mother. The mother explains that she inadvertently dropped the baby onto a "plush" carpet from a distance of two feet while tripping due to fatigue, and the baby immediately became fussy. There was no one around when this happened. The mother has a robust family support system, no other children, and a husband who recently began working as a firefighter who remains on-call throughout the week. Her parents enjoy spending time as a family on the weekends. The mother added that she did not have any prenatal care due to lack of

insurance, but a blood sample was sent to the lab by the pediatrician at the well-baby exam one week after birth due to a "genetic disorder with problems with the bones." The mother says she is unaware of anyone in her family having a disease.

## Diagnostic findings, Part 1

On physical examination (PE), the crown-heel length is 43 cm (normal 51 cm at 38 weeks gestation), and the body weight is 3500 g (normal 3500 g at 38 weeks gestation). The vital signs are blood pressure 90/45 mmHg, heart rate 120 beats per min, respiratory rate 30 breaths per min, and temperature 99.0 °F. The infant's sclerae are slightly blue, pupils are normal, the skull is soft to palpation, deformed limbs are apparent, and no retinal hemorrhages are present. There is tenderness to palpation of the right posterolateral chest wall and right distal humerus without visible bruising. Fractures of the ribs, arm, and possibly the skull in the patient are suspected based on PE. The child is clean, no burns are present on the baby, and no pigeon breast deformity of the chest is noted. The child is inconsolable during this portion of the examination. The mother is concerned for her child.

## Questions/discussion points, Part 1

### What is in the differential diagnosis for suspected childhood fractures?

The differential diagnosis includes child abuse (non-accidental trauma), accidental injury (minor fall, motor vehicle collision (MVC),

cardiopulmonary resuscitation (CPR)), osteogenesis imperfecta (OI), osteopenia of prematurity, rickets, hypophosphatasia, skeletal dysplasia, Menkes disease, *Staphylococcus aureus* osteomyelitis, Caffey disease, and osteopetrosis. A clinically relevant scenario in the case of multiple suspected fractures is recognizing child abuse from a genetic disorder such as OI. Some estimates indicate that approximately 7% of children with physical signs that could be mistaken for child abuse have an underlying medical condition that explains the skeletal findings.[2] Around 20% of child abuse victims were seen by a healthcare professional within 30 days of their homicidal death.[3]

### Describe the clinical manifestations and bone findings in each of the entities in the differential diagnosis

A child under three years of age is 24 times more likely to have fractures stemming from child abuse rather than OI.[4] The number one cause of rib fracture in children less than 12 months old is physical abuse.[5] Posteromedial rib fractures in children have high specificity for child abuse[6] and are significantly rare in OI.[7] High suspicion of child abuse such as clinical or radiographic signs more consistent with physical violence could be excluded by the presence of Wormian bones on conventional radiographs and concomitant blue sclerae.[7] Wormian bones are supernumerary bones most frequently found at the lambdoid or coronal sutures of the skull due to abnormal ossification centers.[8] Old skeletal fractures are generally missed on physical examination, requiring a radiographic survey and description of the stages of healing and all anomalies to be documented when assessing OI versus child abuse.[9]

OI is a heterogeneous connective tissue disorder primarily caused by mutations in the gene coding for type I collagen, affecting the skeleton, sclerae, ears, joints, ligaments, skin, and teeth.[10] Skeletal fragility in OI predisposes to multiple fractures, sometimes the ribs, which explains why OI is high on the differential in suspected child abuse cases. Especially in infants, rib fractures caused postnatally by OI are rare but still possible,[11] requiring careful radiographic examination of the rib fractures to determine their temporal relationship to the encounter's date. Prenatal rib fractures are common in OI, and rib fractures caused by child abuse generally occur after birth. While there are 20 types of OI, congenital rib fractures are more frequently encountered radiologically in OI types II and III.[12,13]

Clinically, OI types I-IV are generally categorized by severity. OI type II is the most severe (death in utero or days after birth[14]), OI type III is severe, OI type IV is moderately severe, and OI type I is the least severe.[15] For example, in the patient described in the clinical vignette who left the hospital and returned to her pediatrician weeks later, OI type II as the diagnosis is less likely than OI types I and IV based on clinical severity. Of those children born with OI type II, incidence rate 1.6 per 100,000 people, as many as 90% die by four weeks of age, and of children born with OI type III, incidence 1.45 per 100,000 live births, about one in four survive to preschool age, and one in four die in the first year of life.[16]

The other possible causes of childhood rib fracture are osteopenia of prematurity (OOP), osteopetrosis, osteomyelitis, and Caffey Disease. OOP typically presents between weeks 5 and 11 after birth.[17] Newborns born at < 28 weeks gestation and very-low birth weight (<1500 g) or extremely low birth weight (<1000 g) infants frequently have OOP.[17] Preterm infants are susceptible to fractures as calcium and phosphate skeletal accretion principally occur during the third trimester of pregnancy.[18] In contrast, a child with osteopetrosis, which is characterized by sclerotic bone, may present with fractures that arise from minor trauma.[19] The child is afebrile with no periosteal reaction of the ribs with soft tissue swelling, fistula, localized erythema, warmth, or swelling at the costochondral junction or posteriorly at the costovertebral angle, ruling out Caffey disease and osteomyelitis.[20–22]

In many cases, the clinical presentation of a child with Menkes disease is apparent by their kinky hair and myoclonic seizures.[23,24] The "kinky hair" in Menkes disease is a conspicuous feature clinically, and the hair appears coarse, sparse, short, twisted, and hypopigmented.[24,25] However, metaphyseal fragmentation and subperiosteal reactive bone on conventional radiographs in Menkes disease could be misinterpreted as stigmata of non-accidental trauma.[26] The findings of Menkes disease, caused by an X-linked recessive mutation in the copper transporter gene *ATP7A,* may overlap with clinical signs of child abuse, including rib fractures.[24] A case report involving a male 5-month-old that presented with multiple healing fractures and posterior rib fracture was initially placed in a custody hold, but the child was proven to have Menkes disease before leaving the hospital.[24] Seizures or fractures may also be associated with child abuse[23] and hypophosphatasia (HPP).[27]

Metabolic bone disease as a cause of childhood rib fracture is prevalent in developing nations or in certain religions where mothers wear face and body coverings, which decreases vitamin D photoconversion and synthesis.[28] Rachitic rosary may be observed in rickets and OI.[29] Fragile bones and fractures are frequently encountered in Menkes disease, vitamin D disorders, and OI; however, in OI, the predisposition to fracture is more common than in these other genetic disorders.[4]

### What are the next steps for the clinician in evaluating the patient in the clinical vignette?

A skeletal survey is a series of radiographs that includes one view of the patient's skull, chest, abdomen, pelvis, upper, and lower extremities. It should be ordered when there is concern for child abuse or an underlying genetic disorder. This clinical suspicion may be based on a discrepancy between the injuries and the history, inappropriate parental affect, and changes in the child's behavior, particularly if the child is less than one year of age. In this case, the baby was dropped only two feet onto a soft surface but had bone deformities and multiple potential fractures. The decision to contact social services must be made.

## Diagnostic findings, Part 2

A radiographic skeletal survey is obtained (Figs. 1–3).

## Questions/discussion points, Part 2

### Describe the findings in the radiographs (Figs. 1–3)

Radiographs reveal generalized osteopenia, Wormian bones, several lateral rib fractures with callus formation, acute oblique right humerus fracture, and bowing and thickening of the bilateral femurs (Figs. 1–3).

These radiographic findings are consistent with osteogenesis imperfecta (OI); however, child abuse has to be considered in any child presenting with multiple fractures.[7] Perinatal rib fractures (Fig. 1), Wormian bones (Fig. 2), femora abnormalities (Fig. 3), and blue sclerae favor the diagnosis of OI type III in this patient.

### What is the most likely diagnosis based on clinical and radiologic information?

The patient most likely has OI based on history, PE, and conventional radiographs.

### What are the most clinically common types of OI and associated defects?

The four main groups of OI were originally described by clinical and radiological findings and pattern of inheritance by Sillence et al. in the 1979 publication *Genetic Heterogeneity in Osteogenesis Imperfecta*.[30] The syndromes were then given a Roman numeral in the order that they appeared in the Sillence et al. publication for entry into the genetics database, Mendelian Inheritance in Man (MIM).[15] OI Types I and IV are similar in that the phenotype is less severe, type II is perinatal lethal (Fig. 4), and type III is progressive deforming.[14] Type I OI usually presents later in childhood with bone abnormalities (Fig. 5) and salient blue sclerae in most cases, and type IV is common variable with
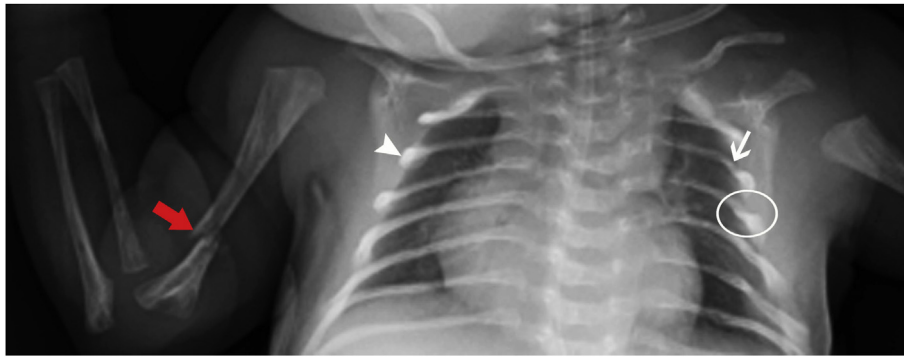
**Fig. 1.** Chest radiograph in a live newborn demonstrates a right humeral fracture (red arrow) and rib irregularities including bowing, healing fracture with callus (arrowhead), suggestion of buckle fractures (white arrow), and fracture with callus distally (open circle).

normal-appearing sclerae.[15] Cardiac defects such as aortic root dilatation and valvular dysfunction in adult patients, and multiple fractures with osteopenic, thin ribs, are more common in OI type III.[15] OI type V was later described by distinctive clinical findings by Glorieux et al., which included calcified radioulnar interosseous membrane and hyperplastic callus.[31] Like OI types I–IV, type V has an autosomal dominant inheritance pattern but is not biochemically related to mutation in the *COL1A1/COL1A2* genes. Clinically, calcification of the forearm interosseous membrane in OI type V significantly increases radial head dislocation.[32] Nursemaid elbow secondary to a parent pulling on the child's arm by the wrist or hand should also be considered in the case of radial head dislocation.

In the past decades since the original Sillence et al. classification, many causal genes have been identified that produce a phenotype consistent with OI. The International Nomenclature Group for Constitutional Disorders ICGH of the Skeleton (INCDS) classification of OI further described OI types using an Arabic numeral 1–5 that aligns phenotypic descriptions, while keeping their original Roman numeral identification.[33] The literature reports as many as 20 types of OI due to molecular genetic testing.[34] The new classification type 1 OI remains non-deforming type I; type 2 encompasses the perinatal lethal and severe form of OI, namely, type II. Type 3 OI includes types III, VI, VIII, IX, and X, the moderate to severe, progressive deforming phenotypes. Type 4 OI includes types IV, VII, and

XI, XII, and XIII moderate severity group. Type 5 includes OI type V with interosseous membrane calcification with or without hypertrophic callus.[33,35] Warman et al. grouped decreased bone density disorders with OI types I–V in the 2010 revision: *Nosology and classification of genetic skeletal disorders* based on the overlap of bone disorders with osteopenia and OI syndromes.[15,36] The OI classifications are summarized in Table 1.[15,33,35,36]

While the general basis for OI classification maintains the Sillence types (OI types I-IV), molecular bases for additional OI types are listed individually, which is why there are 20 or more OI types presently.[36] OI Types I-IX are clinically more common than the rest. Of the most common types, the spectrum of clinical severity from least to lethal perinatally are type I < types IV-VII < types III and IX < type II.[37] The defects, inheritance patterns, and clinical signs of OI types I-IX are summarized in Table 2.[12,14,38–44]

### Describe the differences in a pathologic versus non-pathologic fracture, including some of the factors that may predispose to a pathologic fracture. What factors predispose to pathologic fractures in OI?

A non-pathologic fracture is defined as "a discontinuity of the bone,"[45] whereas pathologic fracture is defined as "Fractures that result from relatively minor trauma to diseased or otherwise abnormal bone."[46] Weakening of bone due to an underlying disease differentiates pathologic fracture from non-pathologic fracture.[14] Non-pathologic fracture generally has a distinctive pattern due to mechanical injury and when bones are soft during infancy, such as greenstick fracture.[14]

The basis for fracture in OI types I-IV is collagen defect caused by a mutation in *COL1A1* or *COL1A2* genes. OI type I is primarily due to insufficient collagen synthesis and sometimes OI type IV.[15] A substantial number of OI types I-IV cases are caused by glycine mutation to another amino acid such as alanine or cysteine near the amino terminus of the peptide chain,[15] which predisposes to pathologic fracture due to the quality of the bone being affected. Collagen fibers are comprised of three left-handed alpha-helical subunits, which form a right-handed coil with glycine residues buried. The backbone of collagen alpha-helices consists of repeating Gly-X-Y amino acids. Glycine mutation causes delayed protein subunit folding and excess post-translational modification,[47] which disrupts the overall collagen fibril structure. Bone achieves its maximum ductility and toughness by sufficient collagen scaffolding.[48] Imperfection in collagen fiber structure due to deficiency or mutation renders OI patients' overall bone architecture weak. Clinically, OI patients present with multiple pathologic fractures, especially in the more severe phenotypes such as OI types II and III. Other causes of pathologic fracture in children are osteomyelitis, benign neoplasm, or osteosarcoma. Still, skeletal fragility in even the mildest forms of OI (OI type I) predisposes to rib fracture postnatally.



**Fig. 2.** Lateral skull radiograph demonstrates Wormian bones (arrow) and poor mineralization of the calvarium.

**Fig. 3.** Anteroposterior radiograph of the lower extremity demonstrates bowing of the left and right femurs (arrows).

### When should a consult for suspected child abuse be ordered?

When there is a discrepancy between the injuries observed and the proposed mechanism, social services should be consulted. If there is high suspicion for an underlying disorder that explains the findings, requesting social services involvement will vary by state. A multidisciplinary approach and legal system are prudent to each suspected child abuse diagnosis and treatment.[3] The American Academy of Family Physicians offers an essential article about patient reporting.[3]

### Discuss the difference between lamellar and woven bone

Lamellar bone is synthesized slowly and is highly organized, whereas woven bone is made rapidly and arranged irregularly.[45] Any woven bone in the adult skeleton is abnormal.[45] Cancellous and cortical bone in adults is lamellar bone, comprised of lamellae sheets, each 3–7 μm thick.[49] Concentric layers of lamellae surround a central Haversian canal. The collagen type I fibers that comprise each lamella are aligned; however, the "pitch" of the collagen fibers between successive lamella is nearly perpendicular, similar to plywood construction.[49] Primary bone, which is the first bone produced during fracture repair or development,



**Fig. 5.** Anteroposterior radiograph of the forearm demonstrates bowing of radius and ulna. Growth arrest lines are noted at metaphases (arrow). A tug lesion is incidentally noted at the diaphysis of the radius (arrowhead).



**Fig. 4.** Osteogenesis imperfecta (OI) type II stillborn baby at autopsy with evident blue sclerae, enlarged calvarium and triangular face.

**Table 1**
Osteogenesis imperfecta (OI) classification.

| INCDS[a] OI Type (Arabic numeral) | OI Type (Roman numeral) | Severity | OI Syndrome | Decreased bone density group |
|---|---|---|---|---|
| Type 1[33,35] | Type I[33,35] | Mild[33,35,36] | Non-deforming[33,36] with blue sclerae[15] | |
| Type 2[33,35] | Type II[33,35] | Severe[33,35,36] | Perinatal lethal[15,33,36] | |
| Type 3[33,35] | Types III, VI, VIII, IX, X[33,35] | Moderate to severe[33,35,36] | Progressive deforming[15,33,36] | Bruck syndrome type 1[33,35,36] |
| Type 4[33,35] | Types IV, VII, XI, XII, XIII[33,35] | Moderate[33,35,36] | Common variable with normal sclerae[15] | |
| Type 5[33,35] | Type V[33,35] | Moderate[33,35,36] | Calcification of interosseous membrane[15,33] | Bruck syndrome types 1 and 2[33,35,36] Osteopetrosis-pseudoglioma syndrome[33,35,36] Idiopathic juvenile osteoporosis[33,35,36] |

[a] INCDS: The International Nomenclature Group for Constitutional Disorders ICGH (International Congress of Human Genetics) of the Skeleton.

**Table 2**
Osteogenesis imperfecta (OI) types I-IX.

| Biochemical defect | OI type | Inheritance pattern | Gene affected (Protein affected) | Clinical features |
|---|---|---|---|---|
| Collagen synthesis and structure[38,39] | I | -Autosomal dominant[14] | *COL1A1/2* (α1 (1) or α2 (1))[14] | -Blue sclerae[14] -Dentinogenesis imperfecta[14] -Postnatal fractures[14] |
| Collagen synthesis and structure[38,39] | II | -Autosomal recessive (most)[14] -Autosomal dominant (some)[14] | *COL1A1/2* (α1 (1), α2 (1))[14] | -Blue sclerae[14] -Death in utero or shortly after birth[14] -Perinatal rib fractures[12] -Crumpled femur[12] |
| Collagen synthesis and structure[38,39] | III | -Autosomal dominant (75%)[14] -Autosomal recessive (25%)[14] | *COL1A2* (α2 (1))[14] | -Blue sclerae that become white[14] -Dentinogenesis imperfecta[14] -Multiple fractures[14] -Thin ribs[12] -Rib fractures[12] -Growth retardation[14] |
| Collagen synthesis and structure[38,39] | IV | Autosomal dominant[14] | *COL1A2* (α2 (1))[14] | -White sclerae[14] -Postnatal fractures[14] -Short stature[14] |
| Bone mineralization[38,39] | V | Autosomal dominant[38,39] | *IFITM5* (BRIL)[39] | -Calcification of interosseous membranes[39,41] -Hyperplastic callus formation[39,42] -Radial head dislocation[39,41] |
| Bone mineralization[38,39] | VI | Autosomal recessive[38,39] | *SERPINF1* (PEDF)[39] | -Moderate to severe skeletal deformity[41] -No fractures at birth[40] -Frequent fractures[40] -Increased alkaline phosphatase[39] |
| Collagen modification[38,39] | VII | Autosomal recessive[38,39] | *CRTAP* (CRTAP)[39] | -White sclerae[41] -Short humeri and femora[43] -Severe rhizomelia[39,42] -Coxa vara[43] |
| Collagen modification[38,39] | VIII | Autosomal recessive[38,39] | *LEPRE1* (P3H1)[39] | -White sclerae[39] -Round face[44] -Vertebral compression fractures[44] -Severe rhizomelia[39] |
| Collagen modification[38,39] | IX | Autosomal recessive[38,39] | *PPIB* (PPIB/CyPB)[38,39] | -Gray sclerae[39] -Multiple long-bone fractures[44] |

lacks concentric lamellae and its collagen fibers, therefore, appear "woven."[50] Woven bone is eventually replaced by secondary bone, lamellar bone, but is limited in OI due to collagen deficiency or mutation. Fracture healing in OI is a clinical concern since lamellar bone is difficult to achieve. Additionally, pseudoarthrosis (a false joint) may occur in nonunion due to pathologic healing in OI patients, leading to limb length discrepancy requiring surgery in some cases.[51]

## Diagnostic findings, Part 3

A histologic section from a patient with OI is shown in Figs. 6 and 7.

## Questions/discussion points, Part 3

### Describe the histologic findings observed in the bone section (Figs. 6 and 7)

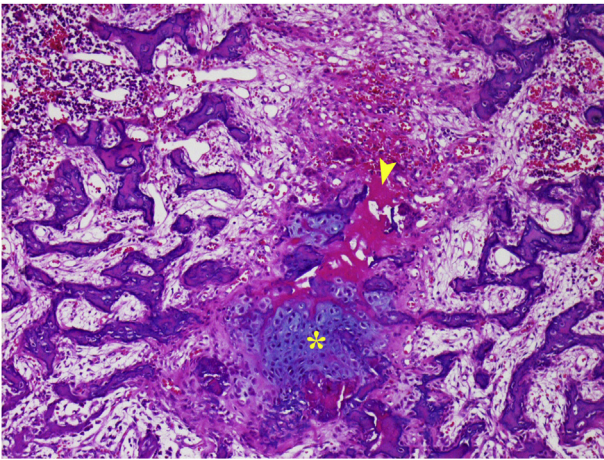The section of long bone shows a markedly thin cortex with hypercellular woven bony trabeculae (Figs. 6 and 7). Healing fractures show irregularly arranged trabeculae with callus formation of woven bone and cartilaginous proliferation (Fig. 6).

### What is the diagnosis based on clinical findings, imaging, and histology?

The microscopic findings in this patient demonstrate reduced lamellar bone and healing fractures with callus formation but normal mineralization. Based on similar long bone histology as the patient in the clinical vignette and clinical severity, including right humeral fracture and bowed and thickened femora, the diagnosis is more consistent with OI type III.

### Describe the histology of some of the most clinically common OI types

Bone volume and trabecular number are generally decreased on histology in OI types I–IV,[39,52,53] and a mixture of woven and lamellar patterns is seen.[54] The fully lamellar state in OI bone tissue is rarely

**Fig. 6.** Section of long bone from a 36-week gestation live born infant showing markedly thin cortex with healing fracture. The physis is not shown but was normal. The trabeculae are thin and hypercellular due to decreased osteoid matrix production. The healing fracture shows callus production consisting of woven bone (arrowhead) and cartilage (*). (H&E, Intermediate power).

reached, which is especially evident in the more severe types of OI as the woven bone matrix predominates.[54] The cellular nature of severe OI bone on histology is described by active osteoblasts, prominent oval osteocytes within a scant matrix, and regularly sized osteoclasts.[54] Perinatal lethal type II-A OI has been histologically characterized by irregular trabeculae with numerous fractures and hypercellularity.[13] The phenotypically less severe OI cases on histology show a propensity for lamellar bone formation, apparent osteoid seams, hypercellularity, and morphologically enlarged osteocytes and osteoblasts accompanying areas of immature woven bone.[54]

On histology, children with OI types I, III, and IV demonstrate normal mineralization with significant reductions in iliac bone cortical width, cancellous volume, trabecular number, and trabecular width.[53] Type IV OI iliac bone show thinner lamellae than controls.[31] The hallmark of type V OI is the "mesh-like lamellation,"[39] whereas buildup of unmineralized osteoid is distinctive in type VI OI.[55] Cortical width in type V OI is decreased compared to type IV, and cancellous bone volume is consistently diminished across types IV, and V.[31] Lamellae are disorganized with a 'fish-scale' appearance under polarized light in OI type VI,
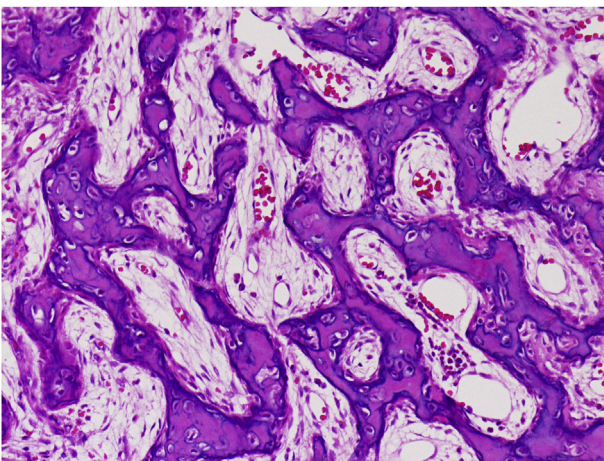


**Fig. 7.** Higher magnification of trabeculae from Fig. 6. The trabeculae are delicate and hypercellular. The trabeculae are calcified but the amount of osteoid is diminished. The osteoid seams are increased. (H&E, intermediate power).

whereas a relatively normal lamellae pattern is observed in type IV OI.[40] A relatively normal lamellae pattern microscopically in OI type IV helps to explain the moderate severity phenotype clinically.

### Describe the Mendelian and non-Mendelian inheritance patterns of osteogenesis imperfecta I-XX

OI is a genetically heterogenous connective tissue disorder, affecting one in 15–20,000 births.[39] The Mendelian inheritance pattern in most OI cases is autosomal dominant, and the rest are primarily autosomal recessive. OI types I–V have an autosomal dominant (AD) inheritance pattern, and only one mutated gene (*COL1A1* or *COL1A2*) is typically present[14]; however, in many cases of AD disorders, two alleles need to be affected to clinically manifest disease. OI types VI-XVIII and XX are autosomal recessive, requiring both copies of the gene to be defective for the person to have OI, but the mother and father do not show clinical signs.[42,56] The skeletal abnormalities associated with OI types I–IV are a result of a dominant negative mutant allele that interferes with normal allele function.[57] OI types II, III, and IV are caused by qualitative defects in type I collagen synthesis, whereas haploinsufficiency mutations lead to the phenotypes seen in OI type I.[55] Because autosomal dominant inheritance only requires one gene to be defective, OI types I–V are more common. It was previously estimated that 90% of OI cases are due to mutations in the *COL1A1* or *COL1A2* genes, which accounts for OI types I–IV.[13]

While OI's inheritance patterns sometimes violate Mendelian laws, there are no other known causes such as environmental or dietary deficiency. In rare instances, parents with no clinical signs of OI may have more than one affected progeny, a phenomenon known as gonadal mosaicism.[56] Gonadal mosaicism occurs due to a postzygotic mutation, which affects gonadal cells during early embryogenesis. Somatic cells remain normal, but gametes have the mutation that causes OI. It is estimated that these abnormal pedigrees occur in 3–5% of cases.[12] A new dominant mutation that happens before the pregnancy in either the responsible sperm or oocyte, which occurs during cell division, is another possible cause of OI.[57] Since the mother or father is not affected by OI, it is also possible that this patient had a new dominant (a type of de novo) mutation, which caused OI. The OI cases that do not arise from parents arise de novo. Some estimates are that de novo mutations account for most perinatal lethal (OI type II) OI cases.[12] The clinical relevance of gonadal mosaicism or de novo mutations is that a family history of recurrent bone fractures is generally absent, like the patient in the clinical vignette, requiring further testing.

The physician may decide to order genetic testing in some cases of OI for definitive diagnosis using a blood sample. An OI-specific genetics panel is ordered, which screens for the common genes mutated, such as *COL1A1* and *COL1A2*. Most clinical genetic tests utilize next-generation sequencing (NGS) presently, which has the advantage of screening multiple genes.[56] NGS may help to diagnose a majority of OI cases.[55]

### Diagnostic findings, Part 4

The blood results previously taken one week after delivery at the well-baby visit for molecular genetic testing are obtained from the lab by request. The genetic results indicate a *COL1A2* gene mutation determined by NGS.

### Questions/discussion points, Part 4

#### What is the utility of genomic analysis in cases of OI versus child abuse?

Although the diagnosis of this patient is consistent with OI in general based on the clinical presentation, imaging, and histology, genomic analysis supports the diagnosis. Additionally, genetic testing for *COL1A1* or *COL1A2* gene mutation may rule out child abuse. Most OI types have *COL1A1/2* mutations. A blood sample was sent at the well-baby visit one

week after birth due to the presence of mildly blue sclerae, a soft skull, and short and deformed limbs. A *COL1A2* mutation is detected by NGS, supporting an autosomal recessive variant of OI as the diagnosis.

### Discuss the possible treatments of osteogenesis imperfecta and associated outcomes

While there is no cure for OI, nutrition, medications, and orthopedic care are all ways to manage the symptoms. The non-pharmacologic therapies include careful intake of nutritional amounts of calcium and vitamin D, routine physical weight-bearing activity, aquatherapy for severe OI cases, and occupational therapy for OI cases involving the upper extremities.[33] The standard of care pharmacotherapy in moderate and severe OI cases has been bisphosphonates such as pamidronate and zoledronic acid.[33] Bisphosphonates are pyrophosphate analogs that work by inhibiting osteoclast resorption of bone to increase bone mineral density and reduce fracture risk and pain.[33] Bisphosphonates given intravenously over orally have an enhanced effect in increasing bone mineral density.[58] While high doses of bisphosphonates to treat cancer have been reported to cause osteonecrosis of the jaw in adults, this has not been reported in children.[59] Denosumab, a human monoclonal antibody targeting the NFκ-B (nuclear factor kappa-B) receptor activator (RANKL) expressed by osteoblasts, inhibits osteoclastic maturation and increases bone density but has had variable results in pediatric patients with OI type VI that responded poorly to bisphosphonate therapy.[59]

### Discuss the possible orthopedic interventions for mild to moderate forms of OI

One of the clinical options for OI patients with osteopenia, high frequency of fracture, and bone deformities is orthopedic intervention.[13] The mainstays in orthopedic treatments for OI type III and IV patients and occasionally in OI type I are intramedullary rod,[13] and supplemental plate using screw fixation to treat nonunions.[41] Anterior cruciate ligament (ACL) tear in an OI type I patient has been successfully managed with bone-patellar tendon-bone allograft instead of autograft to avoid the added patella and tibia donor site defect related to pathologic healing.[60]

### Teaching points

- Osteogenesis imperfecta (OI) is a genetic connective tissue disorder with multiple subtypes causing variable effects on bone and extraskeletal tissues.
- OI and child abuse may have overlapping clinical signs, but radiology, histomorphometry, and molecular genetic tests help confirm the diagnosis.
- OI has significant variability in clinical phenotypes ranging from no obvious signs to perinatally lethal.
- Most patients with OI have a defect in the *COL1A1* and *COL1A2* genes, which encode collagen type I.
- Autosomal dominant inheritance pattern is seen in most patients with OI, but no family history may be present in OI type 2 (perinatal lethal), which commonly arises due to de novo mutations.
- Non-pathologic fracture occurs due to mechanical injury and when bones are soft during infancy, which results in a distinctive pattern such as greenstick. Pathologic fracture is due to an underlying weakness of the bone.
- OI is one cause of pathologic fracture. OI may not have a distinctive pattern of injury, and aberrant healing may be observed as a result of collagen type I defect.
- Glycine mutation predisposes to pathologic fracture in OI due to insufficient scaffolding of type I collagen in bone.
- Imaging findings in OI include osteopenia, long bone deformity, and diaphyseal fractures with hypertrophic callus formation.

- Posterior rib fractures are highly specific for child abuse, while diaphyseal long bone fractures are the most common type of fracture noted in OI.
- The healing of pathological fractures is different from non-pathological fractures. Fractures in OI patients demonstrate hyperplastic callus formation, and pseudoarthrosis may form at the site of healing fractures.
- On histology, many OI subtypes show immature and disorganized matrix.
- Treatments for OI include bone cell modulating pharmacotherapies and orthopedic surgery.

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