Contents lists available at ScienceDirect

Academic Pathology 9 (2022) 100054

Academic Pathology

journal homepage: www.journals.elsevier.com/academic-pathology

Educational Case

Educational Case: Rickets

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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]

Keywords: Bone, Children, Harrison sulcus, Musculoskeletal, Nonneoplastic disorder, Organ system pathology, Osteomalacia, Pathology competencies, Rickets, Varus deformity

Primary objective

Objective MS2.1: Osteomalacia and rickets. Compare and contrast osteomalacia and rickets with respect to pathogenesis and clinicopathologic features.

Competency 2: Organ System Pathology; Topic: MS: Musculoskeletal System; Learning Goal 2: Nonneoplastic Disorders of the Musculoskeletal System.

Patient presentation

A 2-year-old girl presents to her pediatrician with bilateral leg pain. She has been healthy without recent illnesses. Past medical history per the mother, gravida two para two (G2P2), shows the baby was born spontaneously at full term (39 weeks gestation) without complications and breastfed until 18 months. The parents report no history of seizures. Family history is unremarkable for any genetic disorder. The father explains that his daughter has not gained weight and is much shorter than her sister was at this age. The 4-year-old sister was walking by eighteen months, but the patient requires some assistance when bearing weight on her legs. Both children have the same unrestricted diet. Social history indicates that the family spends one weekend every month outside in the sunlight. The patient has not had fevers or rash and is current on all childhood vaccinations.

Diagnostic findings, part 1

The patient's height and weight are 77 cm (normal 87 cm) and 9.5 kg (normal 12.6 kg), Z-score for height- and weight-for-age are −2.35 and −2.46, respectively.[2] The vital signs are blood pressure 96/60 mmHg, heart rate 120 beats per minute, respiratory rate 25 breaths per minute, and temperature 98.5 °F. On physical examination (PE), the patient has no visible skin rash, petechiae, bruises, or lesions. PE of the head, ears, eyes, ears, nose, throat, and neck demonstrates enamel hypoplasia of the primary dentition, white sclerae, healthy gingivae without bleeding, and no palpable cervical lymph nodes. Heart examination reveals no rubs, gallops, or murmurs. Lungs are clear to auscultation, and there is no wheezing. Abdominal examination shows a protruding abdomen with normal bowel sounds and no organomegaly or masses on palpation. Musculoskeletal examination demonstrates bossing of the forehead, severe varus deformity of the lower extremities, exquisite tenderness to palpation of the long bones, and widening of the distal ulna and radius bilaterally, but no hand or foot abnormalities. A soft skull and Harrison sulcus of the chest are evident. Palpable nodularities at the costochondral

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https://doi.org/10.1016/j.acpath.2022.100054
Received 15 December 2021; Received in revised form 11 July 2022; Accepted 15 August 2022, Available online xxxx
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junctions are apparent. Neurological examination shows no focal deficits. Reflexes are intact.

Questions/discussion points, part 1

What is the differential diagnosis for nonneoplastic bone deformities in childhood?

The differential diagnosis includes osteogenesis imperfecta (OI), rickets, Menkes disease, osteopetrosis, Blount disease, physiologic genu varum, scurvy, osteochondrodysplasias, fibrous dysplasia, congenital syphilis, and trauma.

What are the pertinent clinical features for this patient?

Bowlegs or genu varum in a patient older than two years, craniotabes, short stature, palpable nodular foci at the costochondral junction, Harrison sulcus, and bone pain are pertinent clinical examination features present in the patient. Bone pain in children with swollen joints may be observed clinically in vitamin C deficiency (scurvy) and rickets. Harrison sulcus is observed in rickets (or severe asthmatic, chronic malnutrition, and recurrent pneumonia) patients and is due to a protuberant abdomen pushing against the soft ribs at the junction of the diaphragm and rib attachment.[3] This creates a sulcus lateral to the xiphoid process and flaring of the rib cage at their margin inferiorly. Pertinent negatives include a lack of bleeding gingivae, petechiae, or ecchymosis, which lowers our suspicion for scurvy. The lack of blue sclera supports other childhood developmental disorders over common types of OI, such as OI type I, which may present with bone irregularities due to collagen type I defect.[4] The past medical history is negative for seizures, which may be seen in Menkes disease and some cases of rickets.

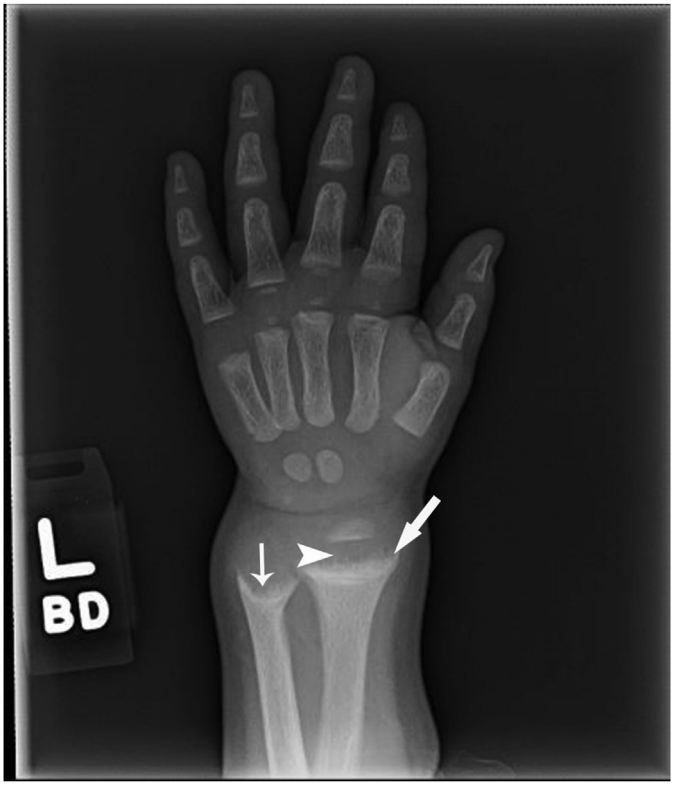

Fig. 1. Frontal view of the left wrist, obtained as part of a rickets bone survey, shows cupping (small arrow) and fraying (large arrow) of the metaphysis of the left radius and ulna. The epiphyseal plate is widened (arrowhead).

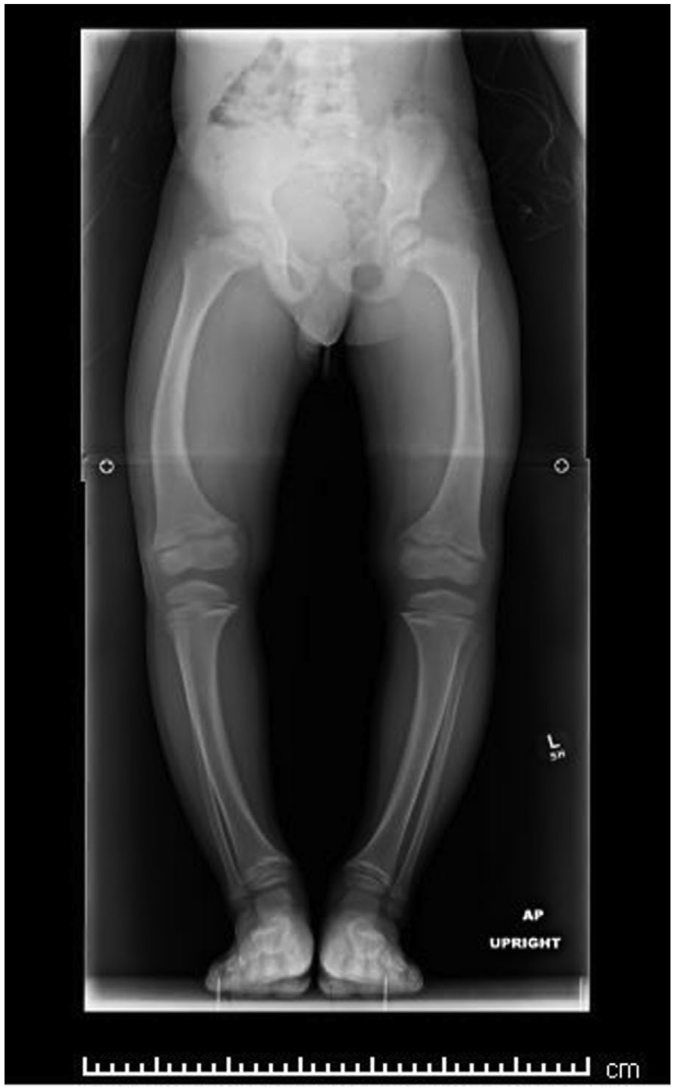

Fig. 2. Upright anteroposterior radiograph of the bilateral lower extremities demonstrates symmetric lateral bowing of the femora and tibias, without leg length discrepancy.

What should be done next?

One should order a bone survey, including anteroposterior (AP) conventional radiographs of the wrist and knee and serum alkaline phosphatase (ALP) level.[5] Based on the clinical presentation, additional laboratory orders include serum parathyroid hormone (PTH), calcium, phosphorus, 25-hydroxyvitamin D, creatinine, and electrolytes.[5] Liver functional tests may provide additional information since it is also involved in active vitamin D metabolism.

Diagnostic findings, part 2

Radiographic findings seen in this patient include bowing of the lower extremities and metaphyseal cupping and fraying, as shown in Figs. 1–4. ALP level is $>$ 5 times the normal level, and phosphorus levels are low. Liver functional tests show no abnormalities, and vitamin D storage levels are normal.

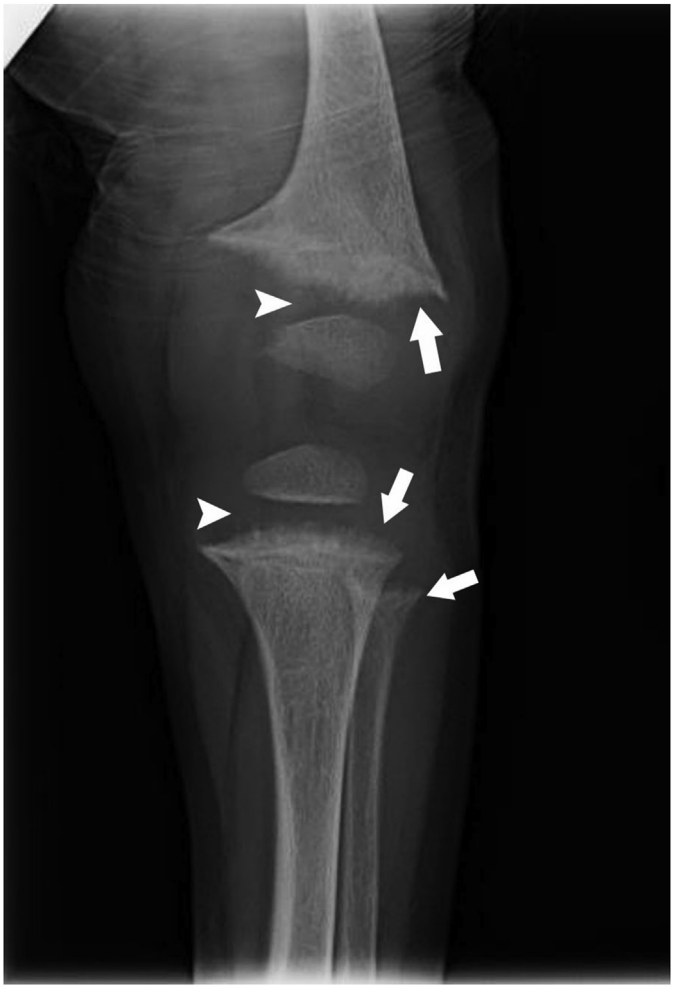

Fig. 3. Anteroposterior radiograph of left lower extremity demonstrating metaphyseal fraying of the femur, tibia, and fibula (arrows). There is a widening of the epiphyseal plates of the femur and tibia (arrowheads).

Questions/discussion points, part 2

What disorder(s) can be ruled out based on the radiographs?

The absence of Erlenmeyer flask deformity, Wimberger ring, and Frankel line are pertinent negatives, which rule out osteopetrosis and scurvy in this patient. On a conventional radiograph, Erlenmeyer flask deformity (circular mid-femur shaft with expanding conical base distally) of the femur may be observed in osteopetrosis.[6,7] Wimberger ring is a circular calcification surrounding the epiphyseal ossification center and Frankel line, a wide zone of provisional calcification, such as at the end of the epiphyses, are both seen in scurvy due to vitamin C deficiency.[8] Osteopetrosis and scurvy are other causes of childhood bone disorders, which manifest as skeletal deformities. OI and rickets may demonstrate osteopenia and bowing of the legs on conventional radiographs; however, OI does not demonstrate cupping and fraying of the metaphysis, which rules out OI (Fig. 5). Additionally, long bone abnormalities were seen in congenital syphilis and usually present at birth or within the first few weeks and demonstrate pathologic fractures or pain, nearly a paralysis clinical picture that is coined "pseudoparalysis of Parrot,"[9] which is not observed in this patient. The normal skin examination, progressive history of disease, and involvement of multiple bones, including bossing of the forehead, help to rule out trauma. Radiographic evidence of polyostotic fibrous dysplasia in this patient is lacking focal radiolucent lesions with thin cortices and a ground-glass appearance.[10]

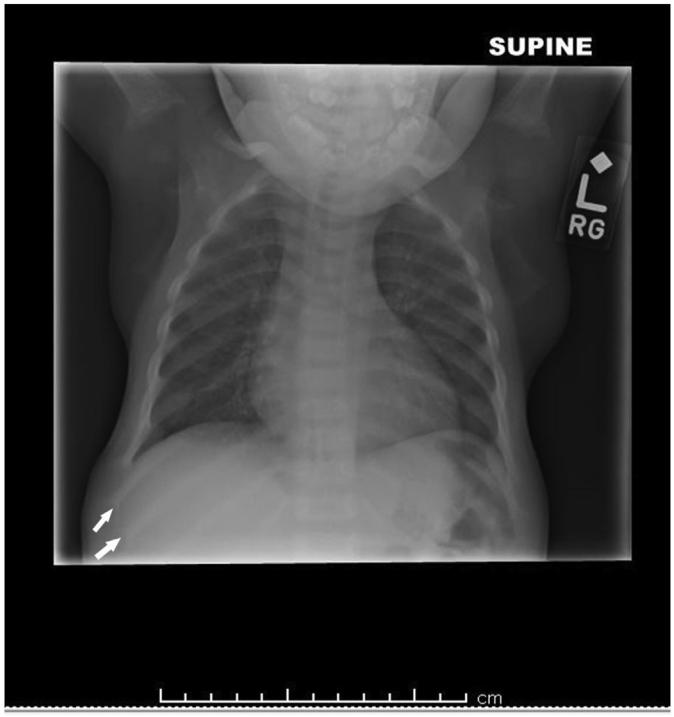

Fig. 4. An anteroposterior radiograph of the chest demonstrates cupping and fraying of the anterior ribs, at the costochondral junction (arrows).

Diagnostic findings, part 3

Table 1 summarizes the laboratory results obtained for our patient.[11–13]

Questions/discussion points, part 3

Outline the role of vitamin D in calcium homeostasis as it relates to bone

The patient has normal calcium but demonstrates hypophosphatemia based on the laboratory results and bone abnormalities on conventional radiographs. These findings could be related to aberrant vitamin D function, which modulates calcium accretion within the skeleton. Breastfed or partially breastfed infants that do not have vitamin D supplement are at increased risk for rickets; however, the laboratory values would indicate a low level of stored vitamin D, which is not seen in this patient. The primary role of vitamin D is calcium-phosphate homeostasis. Calcium accretion in bone facilitates growth and development, especially during third-trimester pregnancy. This patient was born full term; otherwise, prematurity is a clinical consideration for musculoskeletal deformities. In vitamin D metabolism, active vitamin D (1,25-didydroxycholecalciferol) is required for calcium absorption by the gut. Since active vitamin D is needed for calcium and phosphate homeostasis, and therefore, normal bone development, the pathway involved in vitamin D synthesis is essential for the clinician to consider which step(s) may be adversely affected by enzymatic deficiency or abnormalities of receptors, and the subsequent treatment options.

Synthesis of active vitamin D begins with UV-B solar light conversion of 7-dehydrocholesterol to vitamin D3 (cholecalciferol) in the skin, which enters circulation.[14] Sunlight exposure provides an adequate concentration of vitamin D3 for bone development even when the dietary availability of vitamin D is limited.[15] An additional source of inactive vitamin D3 is dietary. Micelles solubilize dietary vitamin D3 in the small intestine lumen, which assembles as part of chylomicrons within intestinal epithelial cells. Lymphatic vessels eventually carry vitamin D3 to

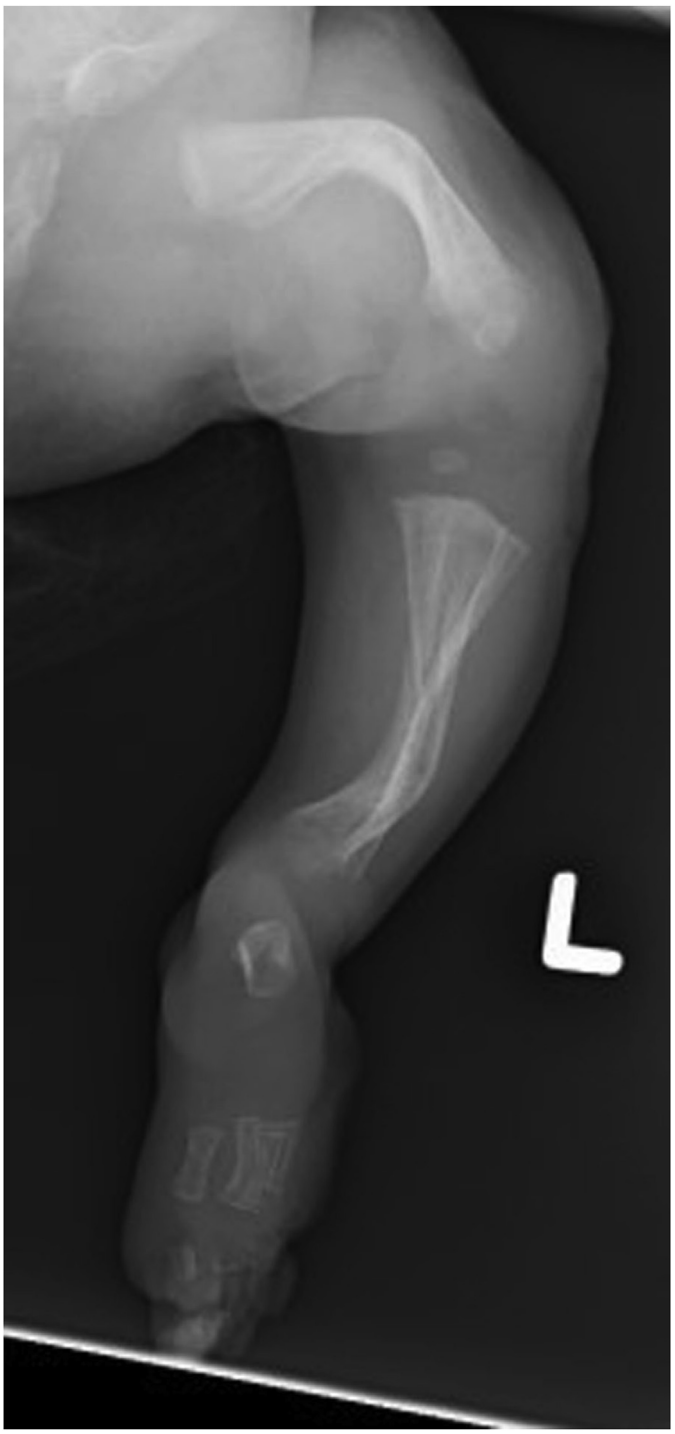

Fig. 5. Anteroposterior radiograph of the left lower extremity demonstrates osteopenia with marked bowing of the femur, tibia, and fibula. The femur may be shortened. There is no fracture or pseudoarthrosis, and no cupping or fraying of the metaphysis is observed.

general circulation. Because vitamin D is a fat-soluble vitamin, transport within the circulation requires a carrier protein, vitamin D transporter protein, or albumin.[16] Secondly, liver metabolism of vitamin D3 results in the synthesis of 25-hydroxy-vitamin D (calcidiol) via the cytochrome p450 enzyme, 25-hydroxylase (*CYP2R1* gene product), the product of which is delivered to the kidneys.[17] The primary clinical marker for vitamin D in storage and circulation is 25-hydroxy-vitamin D.[18] Last, in the conversion of vitamin D to its active form, proximal tubules of the

Table 1
Laboratory test results.

Labs performed on plasma and serum	Patient values	Reference range
Alkaline phosphatase (U/L)	1000	156–369[11]
PTH (pg/mL)	55	10–55[12]
Calcium (mg/dL)	9.8	9.2–10.5[11]
Phosphorus (mg/dL)	1.8	4.3–6.8[11]
25-hydroxy-vitamin D (ng/mL)	25	≥20 (sufficient)[11]
Creatinine (serum) (enzymatic) (mg/dL)	0.30	0.10–0.36[11]
Sodium (mmol/L)	140	136–145[13]
Potassium (mmol/L)	4	3.5–5.5[13]
Chloride (mmol/L)	100	95–105[13]
CO_2 (mmol/L)	25	20–28[13]
Albumin (g/dL)	3.8	3.5–4.7[13]
Alanine aminotransferase (U/L)	20	6–45[13]
Aspartate aminotransferase (U/L)	40	20–60[13]
Bilirubin total/indirect (mg/dL)	0.3/<1.0	0.2–1.0/<1.0[13]
Prothrombin time (PT) (s)	14	11.4–15.8[13]

kidney convert 25-hydroxy-vitamin D to active vitamin D, 1,25-hydroxy-vitamin D (calcitriol), via the mitochondrial cytochrome P450, *CYP27B1* enzyme, and 1α-hydroxylase.[19] Low calcium levels activate PTH (the primary regulator of serum calcium), which increases 1α-hydroxylase synthesis to form calcitriol. 1,25-hydroxy-vitamin D has several systemic effects.

However, 1,25-hydroxy-vitamin D acts on the kidney; nephron distal tubules respond to active vitamin D via the transient receptor potential vanilloid family (TRPV5), resulting in calcium reabsorption.[20] Similarly, active vitamin D forms a heterodimeric complex with nuclear retinoid X receptor (RXR) within intestinal epithelial cells leading to the expression of TRPV6, which facilitates calcium absorption by the duodenum.[19] Aberrant vitamin D signaling due to 1α-hydroxylase deficiency, which causes vitamin D-dependent rickets (VDDR) type I, leads to hypocalcemia, hypophosphatemia, and elevated PTH levels[15] treated with calcitriol.[21] Mutations in the vitamin D receptor cause an increased 1, 25-hydroxy-vitamin D level, which the clinician would not treat with calcitriol. Before treatment, molecular genetic testing to confirm the diagnosis is recommended in clinical practice.[22] Testing for fibroblast growth factor 23 (FGF23) levels is another option clinically and is discussed subsequently.[22]

What are the most common causes of osteomalacia?

In the USA, the most common causes of osteomalacia are liver cholestatic disorders, obstruction of the biliary tree, diseases of the small intestine, and chronic pancreatic insufficiency.[15] These disease etiologies are generally due to the hepatic storage and decreased absorption of vitamin D.

Discuss the pathogenesis of vitamin D deficiency-related bone abnormalities

Rickets is the general term used to describe insufficiently mineralized bone prior to closure of the epiphyseal growth plate in children.[4] Since the epiphyses are closed in adults (due to estrogen across genders), the term osteomalacia is used, not rickets, when describing abnormal bone due to a defect in mineralization.[4] Rickets and osteomalacia can occur due to calcium, phosphate, or vitamin D deficiency.[23] However, the risk for osteomalacia development secondary to dietary calcium deficiency is low, with a few cases known.[24,25] Additionally, 99% of total calcium is stored as a complex with phosphate within bone.[16] A decreased active vitamin D level results in hypocalcemia due to decreased (1) calcium absorption by the intestine, (2) kidney reabsorption of calcium in the distal tubule, and (3) expression of the receptor activator of nuclear factor kappa B-ligand (RANK-L) on osteoblasts. Since RANK-L activates RANK on osteoclast precursors, decreased levels of RANK-L result in reduced osteoclastic resorption of bone and consequently decreased

blood serum calcium. Hypocalcemia clinically is a significant concern in the context of rickets because of seizures and is generally irritating to nerves, lowering the threshold for their action potential. Additionally, calcipenia leads to an unmineralized bone matrix and is seen in rickets or osteomalacia. A systemic response occurs when calcium falls below normal levels with PTH as the primary regulator.

PTH becomes elevated when calcium is low, leading to phosphate excretion by the kidneys through increased expression of *FGF23*, the protein product of which, FGF23, is a critical phosphatonin (hormone regulating phosphorus homeostasis) made by osteocytes, odontoblasts (involved in tooth development), and osteoblasts.[16,23,26] In the early stages of osteomalacia, low calcium leads to secondary hyperparathyroidism, then to phosphaturia, consequently restoring normal calcium levels.[24] The increased FGF23 also reduces intestinal absorption of phosphate. Consequently, hypophosphatemia may remain even when calcium levels return to normal due to FGF23, a characteristic of hypophosphatemic rickets.[16] Later stages of osteomalacia are characterized by hypocalcemia and hypophosphatemia.[24] Normal levels of serum phosphate in this patient's age range from 4.3 to 6.8 mg/dL,[11] whereas the phosphate level seen in the patient in the clinical vignette (1.8 mg/dL) supports hypophosphatemic rickets. The differential for hypophosphatemic rickets includes VDDR, Fanconi syndrome (renal disease of the proximal convoluted tubule causing increased phosphate excretion), renal tubular acidosis, medications, malnutrition, and malabsorption. Phosphopenia results in osteoid (unmineralized matrix) accumulation due to persistent osteoblastic synthesis,[24] which clinically manifests skeletal deformities, especially when beginning to bear weight on the legs.

Diagnostic findings, part 4

A section of bone from a patient with the same disorder is shown in Figs. 6 and 7.

Questions/discussion points, part 4

Describe the histologic findings observed in the bone sections

Figure 6A demonstrates a normal growth plate, and Fig. 6B demonstrates a section of costochondral junction in rickets. Notice overgrowth and disorganization of osteoid tissue (non-mineralized bone matrix). Figure 7 is a high-power field of non-mineralized osteoid. Notice that the osteoid is stained pink. The normal trabeculae of mineralized bone stain violet (basophilic).

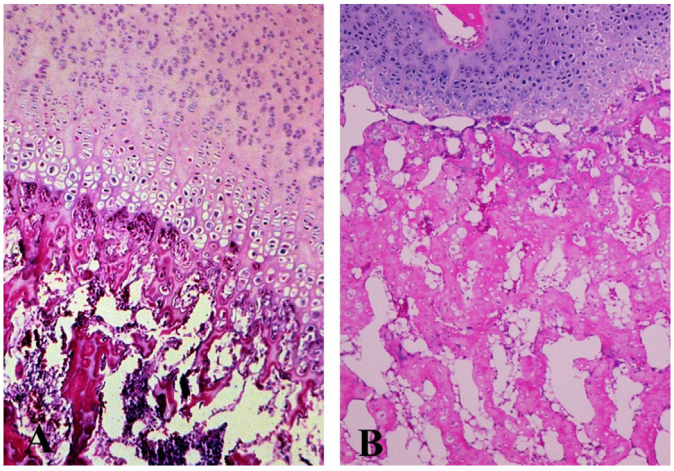

Fig. 6. A) Normal growth plate. (B) Section of costochondral junction in rickets. Notice overgrowth and disorganization of osteoid tissue (non-mineralized bone matrix) (H&E stain, intermediate magnification).

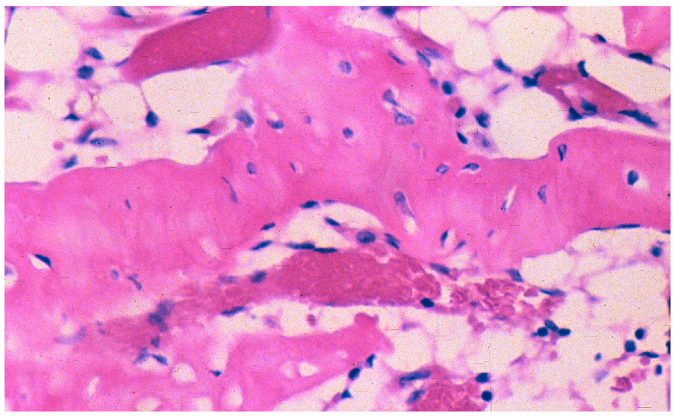

Fig. 7. High-power field of non-mineralized osteoid. Notice that osteoid is stained pink. The normal trabeculae of mineralized bone stain violet (basophilic) (H&E stain, high magnification).

A bone biopsy helps to confirm the diagnosis of rickets; however, the biopsy is rarely used in clinical practice due to imaging, concomitant laboratory results, and molecular genetic testing generally providing sufficient evidence for diagnosing the patient.

Discuss the gross features and microscopic morphology of rickets and osteomalacia

Gross deformities of bone due to abnormal matrix mineralization occur in rickets, such as frontal bossing, Harrison sulcus, craniotabes (widened cranial sutures and fontenelles[24]), shortening and bowing of the extremities, and rachitic rosary of the ribs. Osteomalacia predisposes to fracture of the femoral neck, pubic ramus, vertebral body, and ribs due to weak bone.[15]

Chondrocyte proliferation is unaffected in the rachitic growth plate, but widening occurs due to the failure of apoptosis of the chondrocytes within the hypertrophic cell zone and their replacement by osteoblasts during endochondral bone development.[27] Recall the five chondrocyte zones in the normal growth plate: (1) reserve zone, (2) zone of proliferation, (3) zone of hypertrophy, (4) zone of mineralization, and (5) primary spongiosa.[4] Osteoclasts are active only when osteoid or cartilage is mineralized; the epiphyseal plate thickens without resorption in rickets, hindering growth.[15] This histology explains grossly how rachitic rosary occurs, leading to palpable rib beading on clinical examination and wrist enlargement, both seen on clinical examination in the patient in the clinical vignette. The transition between the epiphyses and new bone microscopically in rickets is disorderly, and cartilage palisades are lost.[28] Abnormal bone trabeculae due to inadequate mineralization are seen on histology in rickets and osteomalacia.[28] Excess unmineralized osteoid surrounded by unaffected trabeculae characterizes osteomalacia microscopically.[28]

Which populations are at risk for rickets?

Rickets due to vitamin D deficiency can occur in breastfed or partially breastfed infants not given vitamin D supplement (foods containing vitamin D), or if the infant does not get enough sunlight exposure.[29] Nutritional rickets is a significant concern globally, including in developed countries with a rising incidence.[30] A risk factor for rickets is living in the northern latitudes above 35°, such as Boston, Massachusetts (42° N), USA, due to decreased UV-B exposure.[30] Race and religious beliefs are substantial in the context of rickets. For example, ethnic minority groups with dark skin have three to 71 times increased risk of rickets due to blockage of UV-B photons by melanin

pigmentation.[31] Burkas, which cover the whole body and veils, have been associated with rickets.[30] Additionally, the winter months predispose to rickets due to the lack of sunlight and vitamin D synthesis.[32] Metabolic bone disease of prematurity, also called rickets of prematurity, is a significant concern for pre-term infants and chronically ill newborn children, occurring in up to 40% of those born very-low birth weight (<1500 g).[33] Generally, rickets of prematurity occurs in children whose skeleton has low amounts of calcium and phosphate stores that is worsened by diminished intake following birth when the skeleton is rapidly growing.[33]

Discuss the genetics of the different inheritable forms of rickets and associated defects

The most common form of hereditary rickets is hypophosphatemic rickets (vitamin D-resistant rickets), an X-linked dominant disorder called XLDHR.[16] In this mode of inheritance, heterozygous females and males with a single copy of the mutant gene on their X-chromosome manifest clinical disease. Random X-linked inactivation in females results in equal gender distribution affected by hypophosphatemic rickets; the incidence is one in 20,000 live births.[16] XLDHR is caused by inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X-chromosome (*PHEX*).[16] *PHEX* is primarily expressed by osteoblasts and plays a significant role in attenuating expression of *FGF23*, and therefore, in preventing phosphate wasting.[34] It is helpful for the physician to recognize that there are relatively few X-linked dominant disorders, and family history sometimes provides essential diagnostic information. For example, in X-linked dominant inheritance, an affected father passes on the mutant gene to all his daughters, and an affected heterozygous mother passes on the mutant gene to half of her sons and daughters. So, while this patient's sister may be unaffected, this patient clinically manifests the genetic disorder. Table 2 includes many of the X-linked dominant disorders.[35–44]

Less common than XLDHR is autosomal dominant type hypophosphatemic rickets (ADHR), in which a gain-of-function mutation in *FGF23* leads to hypophosphatemia.[16] Autosomal recessive forms of hypophosphatemic rickets (ARHR) are other causes of *FGF23*-dependent HR, which both lead to elevations in *FGF23*.[16]

Other causes of hereditary rickets are VDDR which include Types 1A, 1B, and 2A having an autosomal recessive mode of inheritance and Type 2B having an unknown inheritance pattern.[16] Type 3 VDDR arises de novo. VDDR Type 1 is due to decreased conversion of inactive vitamin D3 to its active form, and Type 2 VDDR occurs secondary to vitamin D receptor gene mutations.[22] A gain-in-function mutation in *CYP3A4*, which generally metabolizes drugs, leads to rapid vitamin D metabolite inactivation rendering a deficient state in VDDR Type 3.[19]

What could be ordered to confirm the rickets type?

One should order a hypophosphatemic rickets molecular genetic panel for the patient. A small sample of peripheral blood is sent for next-generation sequencing (NGS), which assesses the most common DNA mutations seen in inherited forms of rickets, including CYP2R1, PHEX, FGF23, and VDR. NGS has the advantage of screening multiple target genes.

Table 2
X-linked dominant disorders.

- Familial hypophosphatemic rickets[35]
- Ornithine transcarbamylase[35]
- Rett syndrome[36]
- X-linked Alport syndrome[37]
- Danon disease[38]
- Fragile X syndrome[39]
- Incontinentia pigmenti[40]
- Giuffre-Tsukahara syndrome[41]
- Goltz syndrome[42]
- X-linked dominant porphyria[43]
- Aicardi syndrome[44]

Diagnostic findings, part 5

The results of the molecular genetic test confirm the diagnosis of X-linked dominant hypophosphatemic rickets with *PHEX* mutation.

Questions/discussion points, part 5

Discuss the possible treatments for rickets and associated outcomes

It is essential to assess which specific form of rickets the patient has. Treating hypophosphatemic rickets with active vitamin D provides no cure. However, an appropriate treatment early on is essential to encourage growth, correct leg deformities, and facilitate tooth mineralization.[22] Since phosphate wasting is a central problem in hypophosphatemic rickets seen in this patient, oral phosphorous supplementation taken multiple times daily is one treatment.[22] Calcitriol is another conventional treatment taken with phosphate supplementation.[22] Additionally, PTH responds to excess phosphate, which means the clinician should monitor PTH during the treatment regimen.[22]

An important consideration in children with rickets is symptomatic hypocalcemia (total calcium <7 mg/dL), which requires prompt treatment. The treatment is slow intravenous (IV) infusion of 100 mL 10% calcium gluconate diluted in 1L of 5% dextrose at 50 mL/hour, 50 mg/kg/day in children, and checking blood calcium every 12 h until calcium is greater than 8.8 mg/dL when the IV treatment stops.[19] However, asymptomatic hypocalcemia is managed by oral vitamin D analogs, including calciferol and calcium supplements.[19]

Teaching points

- Rickets is the term used for skeletally immature individuals, while osteomalacia describes abnormal bone matrix mineralization in the adult population.
- Craniotabes, Harrison sulcus, pigeon breast deformity, rachitic rosary, and bowing of the legs are clinical signs of rickets.
- Nutritional vitamin D deficiency is the most common cause of osteomalacia in adults and rickets before epiphyseal growth plate closure; hypophosphatemic rickets (vitamin D-resistant rickets) is the most common hereditary cause of rickets with an X-linked dominant inheritance pattern.
- Calcium and vitamin D serum levels in hypophosphatemic rickets are normal, and therefore, additional laboratory testing for ALP and skeletal survey may be necessary to further investigate if rickets is the cause of skeletal deformity in children.
- Vitamin D synthesis has several steps, which involve the skin, liver, and kidney. The principle circulating and storage form of vitamin D clinically is 25-hydroxy vitamin D, which is synthesized by the liver. Active vitamin D requires the kidney. The primary regulator of calcium homeostasis is parathyroid hormone, which affects active vitamin D synthesis.
- Conventional radiographs show metaphyseal widening, cupping, and fraying in rickets, which is not observed in other developmental disorders of the skeleton such as osteogenesis imperfecta.
- In rickets, the epiphyseal plate thickens without resorption, which explains severe growth restriction in developing children.
- Rickets occurs prior to epiphyseal closure and therefore it affects children, while osteomalacia happens after growth plate mineralization and fusion in adults.
- Bowing of the legs happens in rickets because of a lack of abnormal growth plate mineralization and persists into adulthood, whereas

osteomalacia affects the hip, spine, and ribs due to softening of the bone after growth plate fusion has occurred.
- Rickets is characterized by abnormal mineralization of osteoid histologically, which predisposes to bowing of the legs when the child begins weight-bearing.
- Widening of the epiphyseal plates on histology with overall disarray of the bone is characteristic of rickets.
- Next-generation sequencing is used to determine the common causes of inherited forms of rickets, which informs various treatment options.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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