Primary objective

Objective MS2.3: Osteoporosis. Distinguish primary from secondary osteoporosis in terms of etiology, pathogenesis, and morphology.

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

Patient presentation

A 76-year-old woman is brought to the emergency department (ED) by ambulance with an externally rotated, abducted, and shortened left lower extremity. The patient says she fell out of bed and could not get up. Prior to the fall, she states she did not have any head trauma, preceding syncopal events, or a history of falls. Her past medical history includes restrictive lung disease for several years but no recent hospitalizations. She has no allergies to medications and has never had an adverse drug reaction. Her only recent medication is bisphosphonate anti-resorptive therapy for a previous vertebral fracture (eight years ago), and she has been on a drug holiday for three years after five years of treatment. Her age of last menstruation was 51 years. Her family history includes lung cancer in her father. There is no family history of hip fracture. She does not smoke, use alcohol, or have a hazardous occupational exposure. Her diet has not recently changed, and there is no recent weight loss. She lives with her daughter and son-in-law and is minimally active, rarely getting sunlight. The review of systems is negative for recent headache, migraine, fevers, cough, urinary changes, hematochezia, melena, or abdominal pain. In the ED, she receives 2.5 mg morphine, intramuscular (IM), on arrival for pain, and is placed on 100% oxygen for some difficulty breathing.

Diagnostic findings, Part 1

The patient's height is 61 inches (154.94 cm), and she weighs 122 pounds (55.34 kg). Her vital signs are blood pressure 148/78 mmHg, heart rate 110 beats per minute, respiratory rate 20 breaths per minute, and temperature of 98.2 °F. Oxygen saturation by pulse oximetry is 88% on room air. Head, ears, eyes, neck, and throat (HEENT) examination demonstrates no head trauma, dry mucous membranes, no palpable thyroid nodules, or glandular enlargement or atrophy; otherwise, the HEENT examination is normal. There is a small abrasion on the left hip, approximately 3 cm in diameter, and ecchymosis with significant swelling of the affected joint; otherwise, the dermatologic examination is unremarkable. Her cardiac examination reveals tachycardia and normal S1, S2 sounds with no rubs, gallops, or murmurs. Her lungs are clear on auscultation, but she is short of breath with tachypnea. Her abdominal examination demonstrates slight protrusion, normal bowel sounds, and no palpable masses or organomegaly. Her musculoskeletal examination demonstrates severe kyphoscoliosis with some tenderness to palpation over the lumbosacral vertebrae. Her left lower extremity is externally rotated, abducted, and shortened. The distal pulse of the left lower limb is 2+ (normal 3+). Her musculoskeletal examination of the right lower extremity is unremarkable, with normal distal pulse 3+, normal range of motion, and strength of 5/5. She has no focal neurologic deficits.
Questions/discussion points, Part 1

What is the significance of the decreased distal pulse?

The decreased distal pulse indicates impaired blood flow, which is concerning for torn retinacular arteries, branches of the medial circumflex femoral artery, and the major blood supply of the femoral head. Avascular necrosis of the femoral head should be a clinical consideration in this scenario as it is common in hip fracture.9

What is the differential diagnosis for the patient?

The differential diagnosis includes hip fracture, hip dislocation, osteoporosis with secondary kyphoscoliosis, osteomalacia, vertebral fracture, and cancer, including metastatic bone disease and multiple myeloma. Hip fracture is ranked high on the differential, but the patient's history and physical examination (PE) cannot exclude an underlying cause, such as metastatic bone disease or osteoporosis. Furthermore, understanding the cause of the patient's fall is prudent for a complete assessment and management to identify any underlying medical conditions.

Define osteomalacia, osteopenia, and osteoporosis and discuss how each of these entities potentially relates to the patient

Osteomalacia is an impairment of bone matrix (osteoid) mineralization in adults, which can only be definitively diagnosed by bone biopsy. Osteomalacia is typically caused by a deficiency in vitamin D or a defect in its metabolism. Bone that undergoes remodeling and is undermineralized in osteomalacia predisposes to fracture, which may be the cause of the patient's presentation. Radiographs demonstrating proximal femur pseudofractures and osteopenia are sometimes observed in osteomalacia. Since the patient's history is significant for rare sunlight exposure, vitamin D deficiency is possible. Osteopenia, a decreased bone mass, may be caused by osteomalacia. Osteopenia, if significant enough to increase fracture risk, is termed osteoporosis.

Osteoporosis has normal bone mineralization but reduced bone mass. Generally, bone resorption is enhanced in osteoporosis compared to bone formation, irrespective of the cause. Bone mass that is –1 to −2.5 standard deviations relative to the peak bone mass of a healthy young adult radiographically is considered osteopenia, whereas osteoporosis is more than −2.5 standard deviations. The decreased bone mass in osteoporosis predisposes to loss of height due to vertebral fractures. Furthermore, vitamin D deficiency in the patient could increase parathyroid hormone (PTH) release (the major regulator of calcium homeostasis), increasing bone resorption, precipitously affecting an osteoporotic state. Since the patient previously used bisphosphonates, a treatment that inhibits bone resorption, it is plausible that she may have severe osteopenia, which predisposed her to conditions described in the past medical history and observed on PE.

Which factors predispose to falls in the elderly?

Many factors predispose to falls in the elderly. Injury secondary to falls in the elderly is common, but the normal aging process does not precipitate falls independently.1 Falling is considered a “geriatric syndrome.” Each year, 30%–40% of individuals over the age of ≥65 years fall at least once.10 Falls account for approximately two-thirds of accidental deaths in individuals ≥65 years.1 There is a two- to six-fold increase in future risk of falls associated with previous falls.1 Hip fracture from a fall increases the likelihood the individual will be placed in a nursing home, which increases the risk of fall roughly three times compared to living in the community.8 However, the patient denies any history of falls. Some other risk factors for falls include dementia, low muscle strength, poor vision, polypharmacy, resting tachycardia, and difficulty rising out of a chair.12 Other cardiovascular, pulmonary and central nervous system disorders are also considerations.

Which factors may have predisposed to possible fractures in the patient?

Metastasis to the bone may predispose to pathologic fracture. Pathologic fracture is a weakness of the bone structure rendering it incapable of resisting everyday biomechanical forces that generally do not cause a fracture. For example, a fall from bed should typically not cause a hip fracture. Multiple myeloma may cause lytic (bone resorbing), “punched out,” radiographic lesions of the pelvis, femur, and vertebral column.11 Weight loss occurs in approximately one-quarter of patients with multiple myeloma, of which the patient's history does not report.14

Furthermore, metastatic tumors involving the skeleton are the most common bone tumors in adults and may predispose to pathologic fracture. Approximately 75% of bone metastases spread from the prostate, breast, kidney, and lung; skeletal metastases are usually multi-focal, involving the axial skeleton. Metastatic skeletal lesions may be lytic radiographically, such as those from the kidney, lung, and gastrointestinal tract. Prostate cancer metastasis generally produces blastic (bone-forming) skeletal lesions, but other types of cancers may cause blastic or mixed (blastic and lytic) skeletal lesions.13 Conventional radiographs of the patient's hip and lumbosacral spine will help prioritize the differential based on if lytic or blastic lesions are present or generalized severe osteopenia is evident.

Other factors that may predispose to pathologic fractures include osteoporosis, which is the cause of a fracture every 3 seconds for someone worldwide.15 The hip and spine are distinct fracture locations for patients with osteoporosis.15 Several national osteoporosis guidelines utilize the Fracture Risk Assessment Tool (FRAX) algorithm, accessible to physicians in the primary care setting.12,16

Which laboratory and imaging tests should be obtained for preadmission workup for suspected hip fracture? Discuss which other imaging studies should be obtained for the patient. Which laboratory tests should be obtained and what results are expected as evidence for osteomalacia?

The clinician should order a chest X-ray (CXR), urinary analysis (UA), complete blood count (CBC), coagulation panel, and electrocardiogram (ECG) as part of the preadmission workup. Conventional radiographs of the hip and lumbosacral spine should also be obtained based on the patient's PE. Since vitamin D deficiency may cause osteomalacia, laboratory results should be obtained, including vitamin D, calcium, phosphophate, PTH, and alkaline phosphatase (ALP). An elevated level of ALP enzyme suggests bone disease (or liver disease). Low serum calcium, phosphophate, 25-hydroxyvitamin D, and elevated PTH and ALP support osteomalacia. In contrast, these laboratory results should be normal in postmenopausal osteoporosis.

Diagnostic findings, Part 2

The patient's CXR demonstrates cardiomegaly without evidence of pneumonia, pneumothorax, or pleural effusion. UA, CBC, and coagulation panel results are summarized in Tables 1–3, respectively. Her ECG

| Laboratory tests | Result | Normal range |
|------------------|--------|--------------|
| Color            | Pale yellow | Pale/dark yellow |
| Transparency     | Clear | Clear/slightly cloudy |
| Specific gravity | 1.030 | 1.005–1.055 |
| pH               | 4.5   | 4.5–8.0      |
| Glucose          | Negative | Negative |
| Ketone           | Negative | Negative |
| Nitrite          | Negative | Negative |
| Blood            | Negative | Negative |
| Leukocytes       | Negative | Negative |
| Urobilinogen     | 0.2   | 0.2–1.0      |
demonstrates tachycardia, a single P wave preceding each QRS complex, and T waves. Table 4 summarizes the laboratory results for vitamin D, calcium, phosphorus, PTH, and ALP enzyme.

The laboratory results are normal, indicating that no further workup is necessary for potentially admitting the patient to the hospital. Moreover, the normal ECG aligns with the patient’s history and supports a non-cardiac etiology as the cause of her fall, such as syncope potentially caused by atrial fibrillation (irregularly irregular rhythm with absent P waves). The imaging, however, demonstrates hip fracture and multiple spinal compression fractures. Figure 1 is a conventional anteroposterior (AP) radiograph of the hip that demonstrates a comminuted displaced left intertrochanteric femur fracture (arrow) with foreshortening and mild medial angulation, with T-score of $-3.9$ on subsequent dual-energy X-ray absorptiometry.

The overall clinical picture for the patient is osteoporosis. The diagnosis of osteoporosis usually occurs after a fracture. Osteoporosis is diagnosed by DEXA radiography, which determines BMD. The World Health Organization (WHO) has specific diagnostic criteria for osteoporosis in postmenopausal women $>50$ years (but not for premenopausal women), which are spinal or hip T-score $<-2.5$; normal BMD is within one SD of the young adult female reference. To diagnose severe established osteoporosis, the criteria are BMD $>2.5$ SDs below the young adult female reference range and one or more fragility fractures. One typical clinical sign reported by an individual with osteoporosis may be loss of height. The patient’s history and PE findings are consistent with osteoporosis based on DEXA score, history of bisphosphonate use, kyphoscoliosis, and hip fracture from a fall out of bed.

**Discuss primary versus secondary osteoporosis. Which type of osteoporosis does the patient have?**

There are two forms of osteoporosis: primary, the most common, and secondary. Primary osteoporosis refers to a precipitous loss of bone mass usually due to hypogonadism and increased age in the absence of recognizable chronic conditions predisposing to bone loss, primarily affecting individuals from 51 to 65 years. Primary osteoporosis is further classified as types I and II. Type I osteoporosis, postmenopausal osteoporosis affects females six times more than males; however, this type is seen in most individuals $>70$ years. Type I osteoporosis is due to decreased estrogen (hypogonadism), primarily affecting postmenopausal women, and type II osteoporosis, senile osteoporosis, occurs twice as often in females than males and is primarily due to aging. Deficiency in calcium, decreased vitamin D, and elevated PTH, which occur due to...
aging, help designate an individual with primary type II senile osteopo-
rosis. Primary osteoporosis may also occur in younger females who are
status post-oophorectomy. In contrast, secondary osteoporosis is due to
established conditions that include celiac disease, cystic fibrosis, Crohn’s
disease, hypercortisolism, myeloma, HIV, rheumatoid arthritis, and
medications. While this list of conditions is not exhaustive, secondary
osteoporosis generally occurs due to chronic conditions that affect bone
mass, and therefore, may affect younger individuals. Based on the
patient’s past medical history and laboratory results, she has primary type
I osteoporosis.

Calculate this patient’s FRAX score using the previously provided BMD for
her left femur using an online tool. Explain when the FRAX score should be
obtained. Discuss some of the limitations of the FRAX score.

The FRAX tool is used to calculate an individual’s ten-year osteopo-
rotic fracture and hip fracture risk. The FRAX probability of fracture is
calculated based on age, sex, weight, height, prior fracture, fractured hip
in parent, smoking, glucocorticoid use, rheumatoid arthritis, secondary
osteoporosis, alcohol consumption, and femoral neck BMD. The FRAX
score for the patient indicates a major osteoporotic ten-year fracture risk
of 45% and hip fracture risk of 24%. The BMD of the femoral neck
should be obtained for females 65 years or older. The FRAX algorithm
requires answering if the individual has secondary osteoporosis based on
whether the individual has type I insulin-dependent diabetes mellitus
(DM), osteogenesis imperfecta, untreated chronic hyperthyroidism, pre-
mature menopause (<45 years), chronic malnutrition, and chronic liver
disease. A possible reason to help explain why type I DM is listed for the
FRAX score calculation and not type II DM is because the former is
associated with a reduced BMD, whereas the latter demonstrates normal
or even increased BMD but diminished bone quality. Therefore, type I
DM predisposes to fracture based on a diminished BMD, which is why
type I DM is included in the FRAX score calculation. Limitations of the
FRAX score include underpredicting the risk of fractures in patients with
recent fractures and individuals at increased fall risk. The FRAX score is
not intended for use in people <50 years or those treated for osteoporosis
previously. Surmise to say that the patient had previous vertebral frac-
tures causing loss of height and kyphoscoliosis, presumably due to
postmenopausal osteoporosis, and was treated with bisphosphonates.

Discuss treatment options for individuals with osteoporosis.

What is a drug holiday?

Bisphosphonates are the first-line treatment for patients with osteo-
porosis. The mechanism of action of bisphosphonates is to inhibit
osteoclast activity. Bisphosphonates are inorganic pyrophosphate an-
alogs that integrate within the hydroxyapatite of bone. Endocytosis of
bisphosphonates by osteoclasts leads to their apoptosis. The accumula-
tion of bisphosphonates within bone after one year of use is what gives an
individual added anti-fracture protection after stopping therapy. Therefore, patients at low to moderate fracture risk may be advised to undergo a drug holiday, stopping treatment for two to three years after three to five years of taking bisphosphonates. Recommendations for high-risk patients (previous osteoporotic fracture or risk for multiple fractures) are to continue taking bisphosphonates or switch to another osteoporosis medication, such as denosumab. Denosumab is a monoclonal antibody that binds to the receptor activator of nuclear factor kappa B ligand (RANKL). RANKL interacts with its receptor on osteoclasts normally, which increases their activity. Therefore, denosumab inhibits osteoclast activity and bone resorption.

**Discuss restrictive lung disease due to kyphoscoliosis in the patient in terms of the pathogenesis**

Due to osteoporosis, vertebral compression fractures in the thoracic spine may lead to kyphoscoliosis, Chest wall deformity resulting from kyphoscoliosis is one cause of restrictive lung disease, which likely explains the patient’s difficulty breathing since her CXR is otherwise clear. Balancing pain control and respiratory effort are a consideration when deciding if I-M morphine should be administered due to its potential for acute respiratory depression.

**Diagnostic findings, Part 3**

A section of vertebrae obtained at autopsy from a patient with a severe form of osteoporosis is shown in Fig. 3. Histology of affected bone is shown in Fig. 4 and Fig. 5A, with comparison to non-osteoporotic bone as shown in Fig. 5B.

**Questions/discussion points, Part 3**

*Describe the gross and histologic findings as shown in Figs. 3, 4, and 5. Compare the histology of osteoporotic to non-osteoporotic bone*

Figure 3 demonstrates the diminished thickness of the vertebral bodies and a compression fracture of the middle vertebral body. There is space widening between the markedly thin trabeculae, and the cortex is inconspicuous. On histology, a low-power view shows a thinned cortex and trabeculae and a lack of trabecular interconnections (Figs. 4 and 5). Compared to a healthy person, bone from individuals with osteoporosis demonstrates changes in the trabecular compartment. The trabecular bone in osteoporosis has a heterogenous bone density and microarchitecture. This is especially true of the vertebrae and proximal femur.

**How are patients typically diagnosed with osteoporosis?**

Bone biopsy in patients with osteoporosis is rarely performed due to its invasiveness, lack of clinician’s technical training to perform the biopsy, pain, cost, few centers available to analyze the bone collection, delays between biopsy and completion of the pathology report, and a gap...
in knowledge regarding the meaning of the morphological results. In the context of vertebral compression fractures, a bone biopsy is not often utilized but may uncover malignancies (metastasis or multiple myeloma) with otherwise normal laboratory results. DEXA assessment is the gold standard clinicians rely upon to diagnose osteoporosis. The Choosing Wisely initiative recommends DEXA to screen for osteoporosis in women with no other risk factors beginning at 65 years and offer other essential information for the clinician. 

Discuss the stages of bone healing

There is a loss of the otherwise contiguous bone structure in a fracture. Fracture healing has three phases: (1) inflammatory, (2) reparative, and (3) remodeling. Age, fracture location, the patient’s overall health, nutrition, and extent of injury affect fracture repair. Fracture repair involves intramembranous ossification (stabilized fracture) or endochondral ossification (non-stabilized fracture). As many as, 10%–15% of the 15 million fractures each year end up with incomplete healing. Osteoporosis, there is a prolonged fracture healing time and impairment in subsequent healing outcomes with decreased BMD and biomechanical properties. The cells and processes involved in earlier bone development and remodeling also facilitate fracture repair. The inflammatory phase involves hematoma formation due to torn blood vessels and the release of clotting factors within two to five days after fracture. In the reparative phase, a fibrocartilaginous mass is formed, known as a pro-callus. Woven bone eventually replaces the pro-callus, forming a hard callus. A microfracture with callus formation is demonstrated on bone histology (Fig. 6). Woven bone appears within seven days in fracture repair. However, woven bone has a haphazard arrangement of collagen type I fibers, hence the name woven. Although this provides initial structural support, maximum strength is achieved through remodeling as lamellar compact or cancellous bone. In adults, any woven bone is abnormal. In the remodeling phase, the bone cortex becomes again contiguous with the non-fractured sites, and a functional blood supply is restored.

Discuss the quality of life after hip fracture in the elderly

Hip fracture is the leading injury diagnosis for admission of the elderly to the hospital. Some estimates are that hip fracture is the cause of mortality in 25% of elderly patients one year after injury. Self-care, ambulation, and mobility are diminished following hip fracture. The reduction in an individual’s quality of life after a hip fracture continues for many years.

Teaching points

- Osteoporosis is a metabolic bone disease in which skeletal mass is histologically normal but reduced, and bone resorption always exceeds formation.
- Osteopenia and fractures of the hip and spine are hallmarks of all types of osteoporosis.
- The normal mineralized to non-mineralized bone ratio is always unaffected by osteoporosis disease progression.
- Risk factors for falls in the elderly include dementia; low muscle strength; poor vision; polypharmacy; resting tachycardia; and difficulty rising out of a chair.
- Risk factors for fracture are low body mass index; previous fracture (vertebral fracture); parent fractured hip; current smoking; glucocorticoids; rheumatoid arthritis; secondary osteoporosis; and alcohol three or more drinks daily.
- The FRAX tool can be used to calculate an individual’s ten-year osteoporotic fracture and hip fracture risk.
- Primary osteoporosis, the most common form of osteoporosis, typically affects postmenopausal women, whereas secondary osteoporosis is due to an underlying disease, medication, or alcohol use.
- Primary osteoporosis is divided into types I and II. Type I osteoporosis, postmenopausal osteoporosis, is related to hypogonadism or estrogen deficiency, whereas type II osteoporosis, senile osteoporosis, is primarily due to aging, and therefore, may be related to a deficiency in calcium, decreased vitamin D, and elevated PTH, which laboratory results may support.
- The WHO diagnostic criteria for osteoporosis in postmenopausal women >50 years are spinal or hip BMD >2.5 SDs below the reference mean for the young adult female (T-score < −2.5).
- Bisphosphonates are inorganic pyrophosphate analogs that chelate to bone and work by inhibiting osteoclasts.
- Kyphoscoliosis secondary to osteoporosis is a cause of restrictive lung disease.
- Bone fracture repair has three phases: (1) inflammatory, (2) reparative, and (3) remodeling.
- Osteoporosis demonstrates delayed fracture healing and reduces mechanical properties.

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