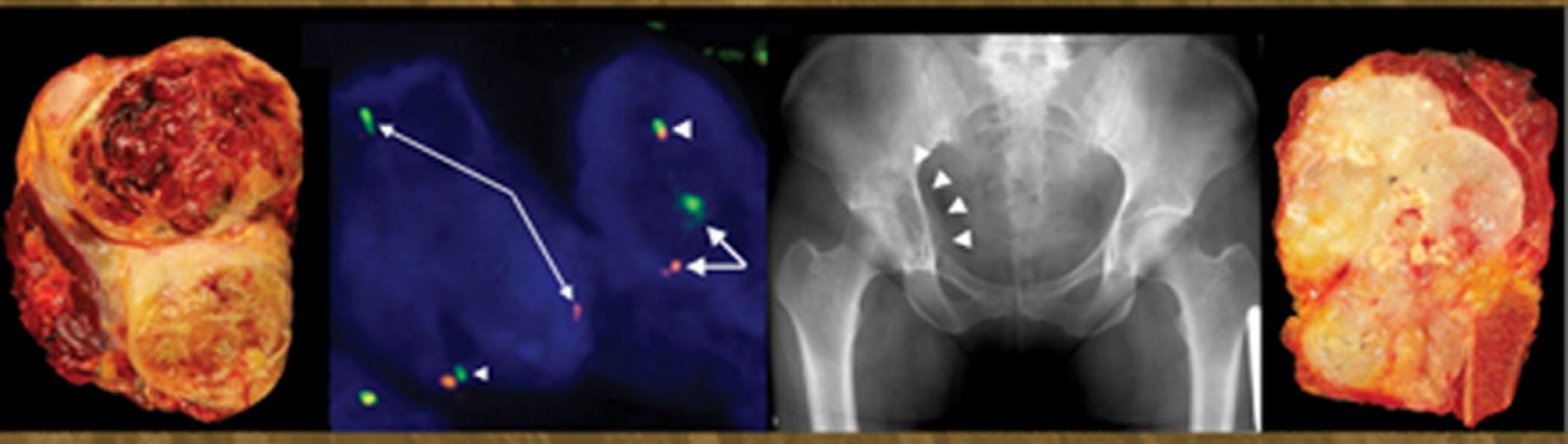
HIGH-YIELD PATHOLOGY

Bone and Soft Tissue Pathology

Andrew Horvai



SAUNDERS
ELSEVIER

HIGH-YIELD PATHOLOGY

Bone and Soft Tissue Pathology

This page intentionally left blank

HIGH-YIELD PATHOLOGY

Bone and Soft Tissue Pathology

Andrew E. Horvai, MD, PhD
Associate Clinical Professor
Department of Pathology
University of California, San Francisco
San Francisco, California

Radiology Editor

Thomas Link, MD
Professor in Residence
Department of Radiology
University of California, San Francisco
San Francisco, California

ELSEVIER
SAUNDERS

ELSEVIER
SAUNDERS

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

BONE AND SOFT TISSUE PATHOLOGY ISBN: 978-1-4377-2520-9

Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

Bone and soft tissue pathology / [editor], Andrew E. Horvai; radiology editor, Thomas Link. — 1st ed.
p. ; cm. — (High-yield pathology)
Includes index.
ISBN 978-1-4377-2520-9 (hardcover : alk. paper)
I. Horvai, Andrew E. II. Link, Thomas M. III. Series: High-yield pathology.
[DNLM: 1. Bone Diseases—pathology. 2. Soft Tissue Neoplasms—pathology. WE 225]
616.71071—dc23 2011040031

Executive Content Strategist: William R. Schmitt
Senior Content Development Specialist: Kathryn DeFrancesco
Publishing Services Manager: Anne Altepeter
Associate Project Manager: Jessica L. Becher
Design Direction: Steve Stave

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To Terrie, Brooke, my dear mother, Gizella, and my late father George
Andrew E. Horvai, MD, PhD

To my wife, Heike, and my parents, Sieglinde and Bruno Link
Thomas Link, MD

This page intentionally left blank

CONTRIBUTORS

Michael Barnes, MD
Neuropathology Fellow
Department of Pathology
University of California, San Francisco
San Francisco, California

Michael Bonham, MD, PhD
Clinical Instructor
Anatomic Pathology
Department of Pathology
University of California, San Francisco
San Francisco, California

Nancy Ciau, MD
Clinical Instructor
Department of Pathology
University of California, San Francisco
San Francisco, California

Vijay George, MD
Clinical Pathology Resident
Department of Pathology
University of California, San Francisco
San Francisco, California

Ryan Gill, MD, PhD
Assistant Clinical Professor
Department of Pathology
University of California, San Francisco
San Francisco, California

Anne Hiniker, MD, PhD
Neuropathology Fellow
Department of Pathology
University of California, San Francisco
San Francisco, California

Andrew E. Horvai, MD, PhD
Associate Clinical Professor
Department of Pathology
University of California, San Francisco
San Francisco, California

Abel Jarell, MD
Dermatopathology Fellow
Department of Pathology
University of California, San Francisco
San Francisco, California

Cindy Jimenez, MD
Surgical Pathology Fellow
Department of Pathology
University of California, San Francisco
San Francisco, California

Ellen Krasik, MD
Clinical Pathology Resident
Department of Pathology
University of California, San Francisco
San Francisco, California

Thomas Link, MD
Professor in Residence
Department of Radiology
University of California, San Francisco
San Francisco, California

Judy Pang, MD
Assistant Professor
Department of Pathology
University of Michigan
Ann Arbor, Michigan

Raga Ramachandran, MD, PhD
Assistant Professor of Clinical Pathology
Department of Pathology
University of California, San Francisco
San Francisco, California

Anatoly Urisman, MD, PhD
Anatomic Pathology Resident
Department of Pathology
University of California, San Francisco
San Francisco, California

Maria Vergara, MD
Surgical Pathology Fellow
Department of Pathology
University of California, Los Angeles
Los Angeles, California

This page intentionally left blank

PREFACE

Specimens from the musculoskeletal system are infrequently encountered by the practicing pathologist. Many of the most common diagnoses, such as traumatic fractures, usually do not require tissue diagnosis. Furthermore, the rarity of bone and soft tissue neoplasms and the disfiguring surgery endorsed by a malignant diagnosis present unique challenges for the pathologist. The difficulty is compounded by the myriad diagnostic entities and the absence of universal classification systems. For the pathologist-in-training, learning the material has been equally demanding. The purpose of this textbook is to present the pathology of bone and soft tissue in a practical, focused, and easily accessible format. The text emphasizes the diagnostic hallmarks of each entity, to allow straightforward, rapid comparison of diagnoses within a single differential. More than 1000 illustrations are provided to supplement the critical details of the text. To achieve this format, discussion of minutiae and controversies is reduced.

In most organ systems, non-neoplastic diseases constitute a significant proportion of diagnoses. Although this is also true of the skeletal system, the pathology of somatic soft tissue is dominated by neoplasms. The resulting disparity between the bone and soft tissue sections of this book, thus, reveals the reality of routine pathology practice rather than omission.

Finally, although this book is intended for pathologists, diseases of bone cannot be diagnosed accurately without evaluation of corresponding radiographic studies. The fundamental radiographic findings for each diagnosis are described and illustrated with high-quality images so that the pathologist can effectively contribute to the multidisciplinary care of the patient.

This volume would not have been possible without the hard work and dedication of the contributors. Thanks especially to Dr. Andrew Folpe and Dr. Carrie Inwards for their assistance and guidance.

Andrew E. Horvai, MD, PhD
Thomas Link, MD

This page intentionally left blank

CONTENTS

I. BONE AND JOINT

A. Metabolic Conditions, 2

Paget Disease, 2
Cindy Jimenez, MD
Osteoporosis, 4
Cindy Jimenez, MD
Osteomalacia, 6
Cindy Jimenez, MD
Rickets, 8
Cindy Jimenez, MD
Osteogenesis Imperfecta, 10
Cindy Jimenez, MD
Hyperparathyroidism, 12
Cindy Jimenez, MD
Serous Fat Atrophy, 14
Cindy Jimenez, MD
Xanthomatosis, 15
Cindy Jimenez, MD
Osteopetrosis, 17
Cindy Jimenez, MD
Ochronosis, 19
Cindy Jimenez, MD
Melorheostosis, 21
Andrew E. Horvai, MD, PhD
Gaucher Disease, 23
Cindy Jimenez, MD

B. Infectious and Inflammatory Conditions, 25

Anatoly Urisman, MD, PhD
Osteoarthritis, 25
Rheumatoid Arthritis, 28
Septic Arthritis, 31
Gout, 33
Other Crystal-Induced Synovitis and Calcium Deposition, 35
Acute Osteomyelitis, 38
Chronic Osteomyelitis, 40
Osteonecrosis, 43
Bone Fracture and Fracture Callus, 45

C. Cystic Lesions, 47

Vijay George, MD
Aneurysmal Bone Cyst, 47
Unicameral Bone Cyst, 50
Intraosseous Ganglion, 52

D. Giant Cell–Rich Lesions, 54

Vijay George, MD
Giant Cell Tumor, 54
Giant Cell–Reparative Granuloma, 57
Brown Tumor, 59
Tenosynovial Giant Cell Tumor, Localized Type, 60
Tenosynovial Giant Cell Tumor, Diffuse Type, 62

E. Mixed Periosteal Lesions, 64

Vijay George, MD
Bizarre Parosteal Osteochondromatous Proliferation, 64
Subungual Exostosis, 66
Florid Reactive Periostitis, 68

F. Cartilage-Forming Lesions, 70

Andrew E. Horvai, MD, PhD
Solitary Osteochondroma, 70
Multiple Hereditary Exostoses, 73
Enchondroma, 75
Multiple Chondroma Syndromes (Ollier Disease, Maffucci Syndrome), 78
Periosteal Chondroma, 80
Synovial Chondromatosis, 82
Chondro-Osseous Loose Body, 85
Chondromyxoid Fibroma, 87
Chondroblastoma, 89
Conventional Intramedullary Chondrosarcoma, 92
Chondrosarcoma of the Small Bones of the Hands and Feet, 96
Periosteal Chondrosarcoma, 99
Secondary Chondrosarcoma, 101
Clear Cell Chondrosarcoma, 103
Dedifferentiated Chondrosarcoma, 105
Mesenchymal Chondrosarcoma, 108

G. Bone-Forming Lesions, 111

Maria Vergara, MD
Bone Island, 111
Osteoid Osteoma, 112
Osteoblastoma, 114
Conventional Osteosarcoma, 116
Small Cell Osteosarcoma, 119
Telangiectatic Osteosarcoma, 121
High-Grade Surface Osteosarcoma, 123
Post-Treatment Osteosarcoma, 125
Parosteal Osteosarcoma, 127
Periosteal Osteosarcoma, 130
Low-Grade Central Osteosarcoma, 132
Chondroblastoma-Like Osteosarcoma, 134

H. Notochordal Tumors, 136

Benign Notochordal Cell Tumor, 136
Andrew E. Horvai, MD, PhD
Chordoma, 138
Michael Barnes, MD

I. Fibrous Lesions, 140

Maria Vergara, MD
Fibrous Dysplasia, 140
Osteofibrous Dysplasia, 143
Desmoplastic Fibroma, 145
Nonossifying Fibroma, 147
Ossifying Fibroma, 149

J. Vascular Lesions, 151

Hemangioma, 151
Andrew E. Horvai, MD, PhD
Synovial Hemangioma, 154
Andrew E. Horvai, MD, PhD
Epithelioid Hemangioma, 156
Andrew E. Horvai, MD, PhD
Epithelioid Hemangioendothelioma, 158
Ryan Gill, MD, PhD
Angiosarcoma of Bone, 160
Andrew E. Horvai, MD, PhD
Massive Osteolysis, 163
Andrew E. Horvai, MD, PhD

K. Ewing Sarcoma, 165

Cindy Jimenez, MD

L. Hematopoietic Lesions, 168

Judy Pang, MD
Primary Osseous Lymphoma, 168
Acute Myeloid Leukemia, 170
Plasmacytoma, 172
Langerhans Cell Histiocytosis, 174
Mastocytosis, 176

M. Undifferentiated Pleomorphic Sarcoma of Bone, 178

Anatoly Urisman, MD, PhD

N. Adamantinoma, 181

Anatoly Urisman, MD, PhD

O. Lipomatous Tumors, 184

Andrew E. Horvai, MD, PhD
Intraosseous Lipoma, 184
Synovial Lipomatosis, 186

P. Carcinoma, 188

Anatoly Urisman, MD, PhD
Metastatic Carcinoma, 188
Squamous Cell Carcinoma Arising in a Draining Sinus of Chronic Osteomyelitis, 191

II. SOFT TISSUE

A. Inflammatory and Pseudosarcomatous Myofibroblastic Proliferations, 194

Abel Jarell, MD
Nodular Fasciitis, 194
Proliferative Myositis and Proliferative Fasciitis, 197
Ischemic Fasciitis, 199
Postoperative Spindle Cell Nodule, 201
Necrotizing Fasciitis, 203

B. Fibrosing Lesions and Fibromatoses, 205

Abel Jarell, MD
Elastofibroma, 205
Desmoplastic Fibroblastoma, 207
Hypertrophic Scar, 209
Keloid, 211
Fibrous Hamartoma of Infancy, 212
Gardner Fibroma, 214
Nuchal Fibroma, 216
Fibromatosis Colli, 217
Calcifying Aponeurotic Fibroma, 219
Fibroma of Tendon Sheath, 221
Superficial Fibromatosis, 223
Deep Fibromatosis, 225
Inclusion-Body Fibroma, 228
IgG4-Related Sclerosing Disease, 230

C. Myofibroblastic Tumors, 232

Raga Ramachandran, MD, PhD
Myofibroblastoma (Mammary Type), 232
Inflammatory Myofibroblastic Tumor, 234
Myofibroma and Myofibromatosis, 237
Intranodal Myofibroblastoma, 239
Myofibroblastic Sarcoma, 241

D. Perivascular Tumors, 243

Michael Barnes, MD
Glomus Tumor, 243
Glomuvenous Malformation, 245
Myopericytoma, 246

E. Fibroblastic and Fibrohistiocytic Tumors, 248

Reticulohistiocytoma, 248
Ellen Krasik, MD
Juvenile Xanthogranuloma, 250
Ellen Krasik, MD
Benign Fibrous Histiocytoma, 252
Ellen Krasik, MD
Angiomatoid Fibrous Histiocytoma, 255
Ellen Krasik, MD
Plexiform Fibrohistiocytic Tumor, 257
Nancy Ciau, MD
Superficial Acral Fibromyxoma, 259
Ellen Krasik, MD
Superficial Angiomyxoma, 261
Ellen Krasik, MD
Dermatofibrosarcoma Protuberans, 262
Ellen Krasik, MD
Giant Cell Fibroblastoma, 264
Abel Jarell, MD
Fibrosarcoma Arising in Dermatofibrosarcoma Protuberans, 266
Ellen Krasik, MD
Adult Fibrosarcoma, 268
Andrew E. Horvai, MD, PhD
Infantile Fibrosarcoma, 270
Andrew E. Horvai, MD, PhD
Sclerosing Epithelioid Fibrosarcoma, 272
Michael Bonham, MD, PhD
Low-Grade Fibromyxoid Sarcoma, 273
Michael Bonham, MD, PhD
Atypical Fibroxanthoma, 275
Nancy Ciau, MD
Intramuscular Myxoma, 277
Nancy Ciau, MD
Myxofibrosarcoma, 279
Nancy Ciau, MD

F. Adipose Tumors, 281

Andrew E. Horvai, MD, PhD
Lipoblastoma, 281
Lipoma and Lipomatosis, 283
Angiolipoma, 285
Neural Fibrolipoma, 286
Hibernoma, 287
Chondroid Lipoma, 289

Spindle Cell and Pleomorphic Lipoma, 290
Well-Differentiated Liposarcoma and Atypical Lipomatous Tumor, 292
Dedifferentiated Liposarcoma, 295
Myxoid and Round Cell Liposarcoma, 298
Pleomorphic Liposarcoma, 300

G. Smooth Muscle Tumors, 302

Andrew E. Horvai, MD, PhD
Angioleiomyoma, 302
Pilar Leiomyoma, 304
Leiomyoma of Deep Soft Tissue, 305
Leiomyosarcoma of Soft Tissue, 306
Vascular Leiomyosarcoma, 309
Epstein-Barr Virus–Associated Smooth Muscle Tumor, 311

H. Genital Stromal Tumors, 313

Vijay George, MD
Fibroepithelial Polyp, 313
Angiomyofibroblastoma, 315
Cellular Angiofibroma, 317
Aggressive Angiomyxoma, 319

I. Skeletal Muscle Tumors, 321

Judy Pang, MD
Adult Rhabdomyoma, 321
Fetal Rhabdomyoma, 323
Genital Rhabdomyoma, 324
Alveolar Rhabdomyosarcoma, 325
Embryonal Rhabdomyosarcoma, 327
Pleomorphic Rhabdomyosarcoma, 330

J. Nerve and Nerve Sheath Tumors, 332

Traumatic Neuroma, 332
Michael Barnes, MD
Schwannoma, 334
Anne Hiniker, MD, PhD
Ancient Schwannoma, 336
Anne Hiniker, MD, PhD
Ganglioneuroma, 338
Anne Hiniker, MD, PhD
Neurothekeoma, 340
Michael Barnes, MD
Cellular Schwannoma, 343
Anne Hiniker, MD, PhD
Neurofibroma, 345
Anne Hiniker, MD, PhD
Plexiform Neurofibroma, 348
Anne Hiniker, MD, PhD
Palisaded Encapsulated Neuroma, 350
Anne Hiniker, MD, PhD
Perineurioma, 352
Michael Barnes, MD
Malignant Peripheral Nerve Sheath Tumor, 353
Anne Hiniker, MD, PhD
Malignant Triton Tumor, 356
Anne Hiniker, MD, PhD
Granular Cell Tumor, 358
Anne Hiniker, MD, PhD
Malignant Granular Cell Tumor, 360
Anne Hiniker, MD, PhD
Neuroglial Heterotopia, 362
Anne Hiniker, MD, PhD
Neuroblastoma, 364
Anne Hiniker, MD, PhD
Esthesioneuroblastoma, 366
Anne Hiniker, MD, PhD
Paraganglioma, 368
Anne Hiniker, MD, PhD
Melanotic Neuroectodermal Tumor of Infancy, 370
Andrew E. Horvai, MD, PhD

K. Vascular Tumors, 372

Ryan Gill, MD, PhD
Papillary Endothelial Hyperplasia, 372
Pyogenic Granuloma, 374
Arteriovenous Malformation, 376
Capillary Hemangioma, 378
Cavernous Hemangioma, 380
Lymphangioma, 382
Epithelioid Hemangioma, 384
Kimura Disease, 385
Spindle Cell Hemangioma, 387
Sinusoidal Hemangioma, 389
Epithelioid Hemangioendothelioma, 390
Hobnail Hemangioendothelioma, 393
Angiosarcoma, 395
Intimal Sarcoma, 398
Kaposi Sarcoma, 400
Kaposiform Hemangioendothelioma, 403

L. Bone and Cartilage Tumors of Soft Tissue, 405

Andrew E. Horvai, MD, PhD
Soft Tissue Chondroma, 405
Extraskeletal Myxoid Chondrosarcoma, 407
Nuchal Fibrocartilaginous Pseudotumor, 409
Myositis Ossificans, 411
Ossifying Fibromyxoid Tumor, 414
Soft Tissue Osteosarcoma, 417

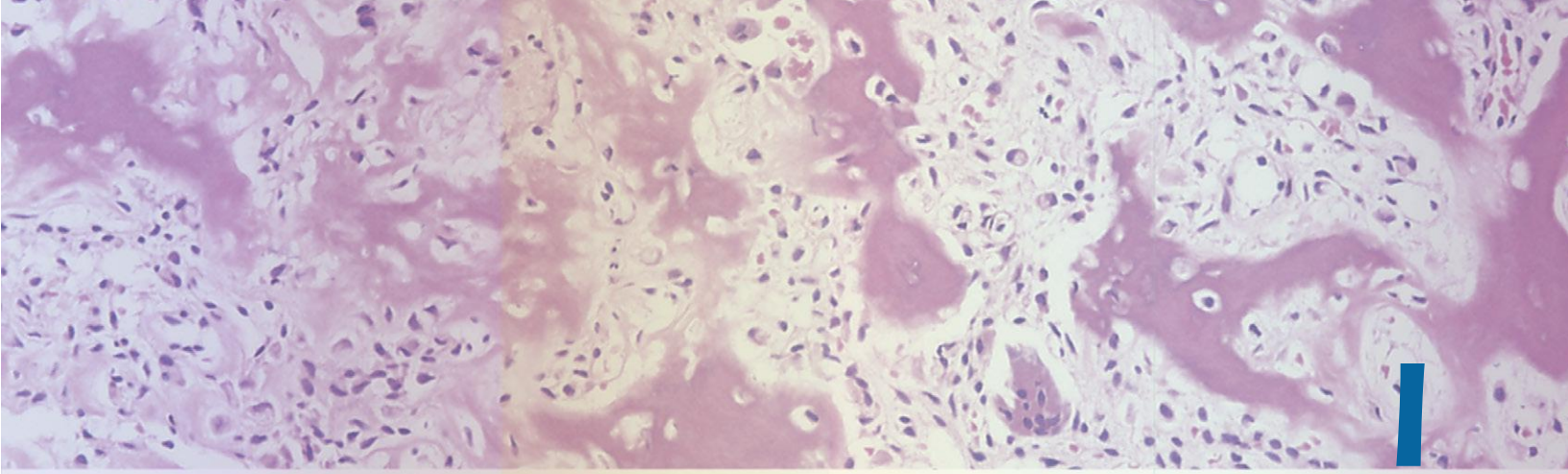
M. Perivascular Epithelioid Cell Neoplasms, 419

Andrew E. Horvai, MD, PhD

N. Tumors of Uncertain Lineage, 421

Pleomorphic Hyalinizing Angiectatic Tumor of Soft Parts, 421
Michael Bonham, MD, PhD
Soft Tissue Myoepithelioma, 423
Michael Bonham, MD, PhD
Alveolar Soft Part Sarcoma, 426
Michael Bonham, MD, PhD
Clear Cell Sarcoma, 428
Michael Bonham, MD, PhD
Synovial Sarcoma, 430
Michael Bonham, MD, PhD
Extrarenal Rhabdoid Tumor, 433
Michael Bonham, MD, PhD
Epithelioid Sarcoma (Proximal and Distal), 435
Michael Bonham, MD, PhD
Desmoplastic Small Round Cell Tumor, 438
Michael Bonham, MD, PhD
Primitive Neuroectodermal Tumor (Ewing Sarcoma), 440
Michael Bonham, MD, PhD
Giant Cell Tumor of Soft Tissue, 442
Michael Bonham, MD, PhD

Undifferentiated Pleomorphic Sarcoma, 444
Michael Bonham, MD, PhD
Phosphaturic Mesenchymal Tumor, 446
Andrew E. Horvai, MD, PhD
Myxoinflammatory Fibroblastic Sarcoma, 448
Michael Bonham, MD, PhD
Ectopic Hamartomatous Thymoma, 451
Andrew E. Horvai, MD, PhD
Solitary Fibrous Tumor and Hemangiopericytoma, 453
Michael Barnes, MD



I

BONE AND JOINT

PAGET DISEASE

Definition and synonyms
- A chronic skeletal bone disorder due to overactivation of osteoblasts and osteoclasts with resultant abnormal remodeling of bone (osteitis deformans)

Clinical features
Epidemiology and presentation
- Bone pain, warmth, tenderness, and arthritis
- Localized skeletal deformity and spinal stenosis
- Stress fractures with minimal trauma
- Headaches, deafness, and increased hat size with skull involvement
- Markedly elevated serum alkaline phosphatase with normal calcium and phosphorus

Prognosis and treatment
- Usually asymptomatic; may be focal, multifocal, and progressive
- Severe forms show marked deformity, intractable pain, neurologic symptoms, and cardiac failure
- One to 3% of cases complicated by sarcoma (osteosarcoma, undifferentiated sarcoma)
- Asymptomatic patients require no treatment except in extensive skull involvement
- Symptomatic treatment with analgesics
- Bisphosphonates and calcitonin medical therapy

Radiology
- Osteolytic change in the early phase
- Initial lesions may be destructive and radiolucent, especially in the skull (osteoporosis circumscripta)
- Later bone deformity, thick cortical bone, coarsening of bone trabeculae, and loss of demarcation between cortical and trabecular bone
- Window frame appearance of vertebral bodies: increased density of the vertebral body periphery and accentuation of the trabeculae in the body
- Hot on bone scans unless it is in the inactive phase
- Stress fractures with multiple fissures in long bones at later stages
- Focal bone proliferation with malignant transformation

Pathology
Gross
- Bone is hyperemic with distortion of the normal contour and structure

Histology
- Osteolytic phase shows primarily osteoclastic activity with increased multinucleated osteoclasts mimicking hyperparathyroidism
- Active or mixed phase shows increased osteoclastic and osteoblastic activity with remodeling, fibrosis, and osteoid formation
- Thick and thin bone trabeculae are often present
- Sclerotic phase shows prominent irregular, wavy cement lines that reflect abnormal remodeling and may be the only feature in inactive disease
- Reticulin stain highlights disorganization of lamellar bone

Main differential diagnosis
- Hyperphosphatasia
- Polyostotic fibrous dysplasia
- Chronic osteomyelitis

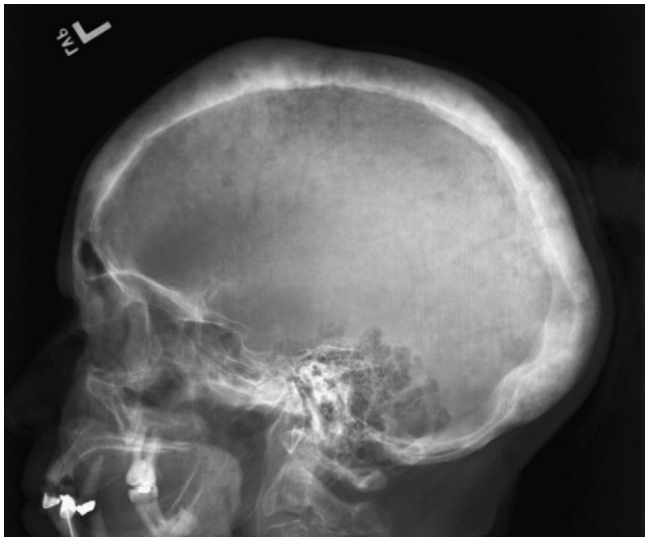


Fig 1. Lateral radiograph of the skull in a patient with Paget disease showing thickening of the cortex with increased sclerosis mixed with lytic areas, also referred to as a cotton-wool appearance.

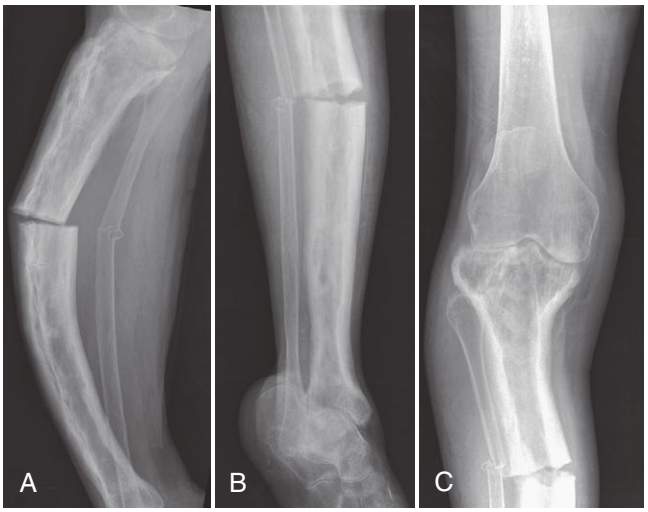


Fig 2. Lateral radiograph of the right tibia and fibula (**A**) and anteroposterior radiographs of the ankle (**B**) and knee (**C**). Note transverse fractures in the tibia and fibula, which are common because bone is inherently weak. There is marked cortical thickening of the tibia extending from the articular surface of the knee to the articular surface of the ankle. Deformity of the right tibia with anterior and lateral bowing is also shown.

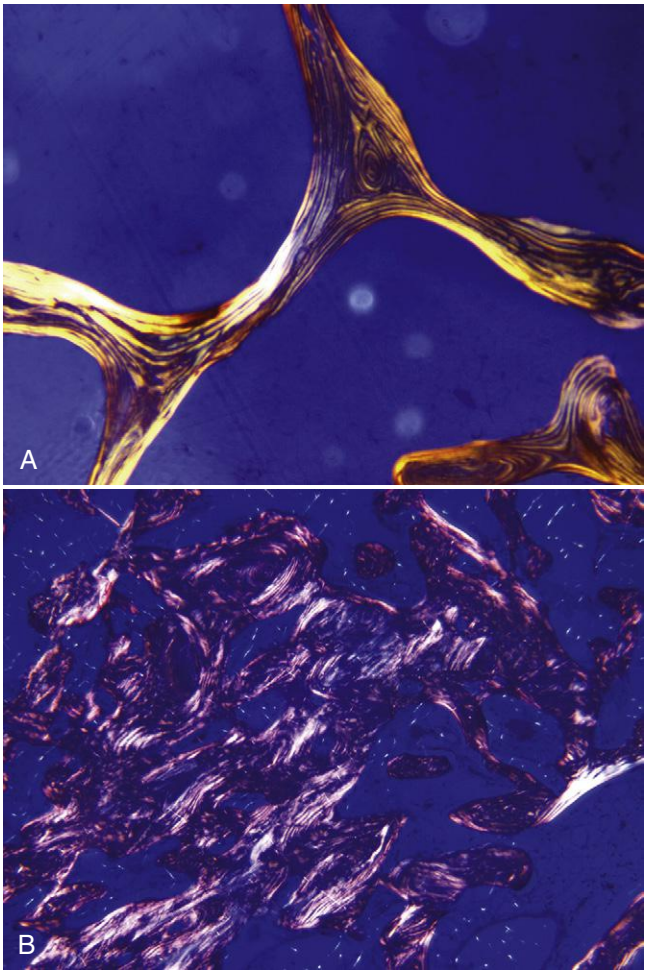


Fig 3. Polarized light histopathology of normal bone (**A**) and bone from a patient with Paget disease (**B**). In Paget disease, the laminar sheetlike orientation is disrupted, leading to less refractile, interrupted collagen.

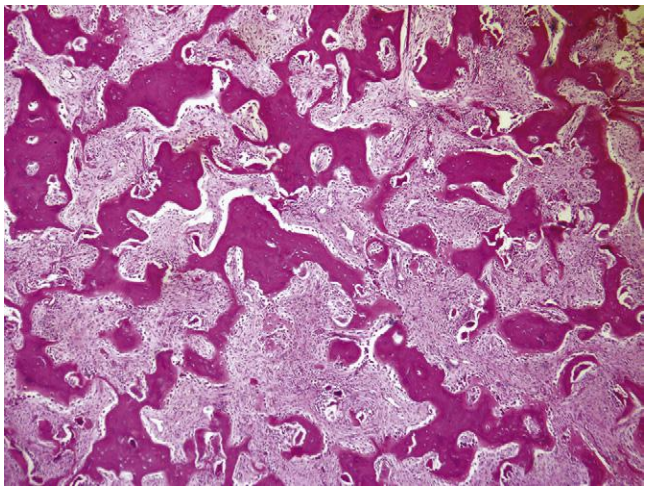


Fig 4. Scanning magnification in a patient with Paget disease showing thick and thin irregular trabecular bone, extensive fibrosis, and increased vascularity of bone marrow and irregular cement lines.

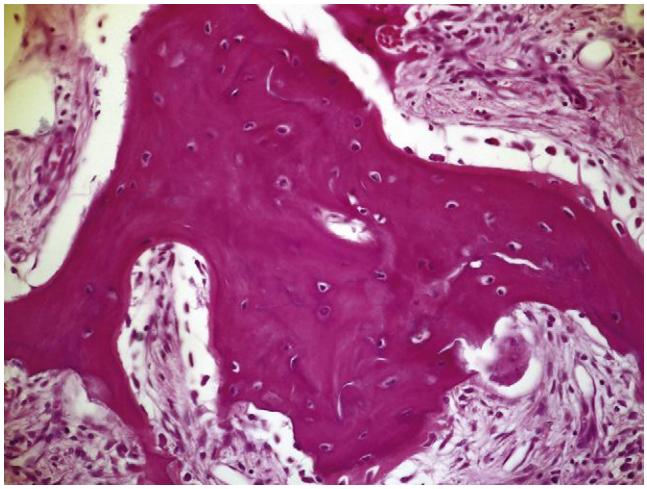


Fig 5. Higher magnification in a patient with Paget disease showing thick and prominent trabecular bone with large multinucleated osteoclasts.

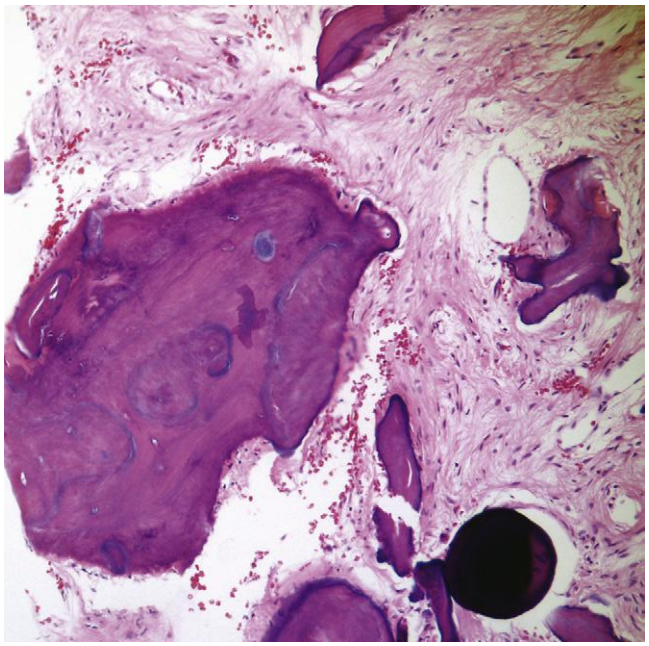


Fig 6. In the sclerotic phase of Paget disease bone is formed with thickened, irregular trabeculae with osteoid seams creating a mosaic pattern of cement lines. This reflects prior incidences of bone resorption and formation.

OSTEOPOROSIS

Definition and synonyms

- Decrease in bone density of normally mineralized bone; the World Health Organization defines it as a bone mineral density that is 2.5 standard deviations (SD) below the mean peak value in young adults (porous bone)

Clinical features

Epidemiology

- Most common metabolic bone disease
- Most common in patients older than 50 years
- Postmenopausal women are affected because of estrogen deficiency
- Secondary causes include endocrine disorders, gastrointestinal disturbances, drugs, and immobilization
- Risk factors include smoking, caffeine, and alcohol consumption
- 1.5 million fractures per year leading to 37,500 deaths per year in the United States

Presentation

- Back pain, loss of height, thoracic kyphosis, fractures with minimal trauma
- Vertebral crush fractures and spontaneous fractures in severe form
- Cancellous compartment of vertebral bone, pelvis, and wrist most commonly affected
- Normal serum parathyroid hormone, calcium, phosphorus, and alkaline phosphatase

Prognosis and treatment

- Increased mortality rate due to complications of fractures; better prognosis with early maintained treatment
- Vitamin D and calcium supplementation
- Bisphosphonates increase bone thickness and lower the risk for fractures and are used for prevention and treatment
- Selective estrogen receptor modulators (raloxifene) act on bone to slow resorption by osteoclasts

Radiology

- Substantial bone loss (approximately 30% to 40%) must occur before routine radiographs are sensitive enough to detect
- Techniques to measure bone mineral density include dual energy X-ray absorptiometry and quantitative CT
- A bone mineral density 2.5 SD below the mean of a young adult is considered osteoporosis (T score of –2.5); between 1 and 2.5 SD below the mean is osteopenia
- Conventional radiographs show cortical thinning, increased radiolucency, vertebral compression, widening and swelling of intervertebral disks
- Three types of spinal fractures are identified in advanced disease: wedge fractures, biconcave fractures, and crush fractures
- The most severe complication is proximal femur fracture, typically femoral neck and intertrochanteric

Pathology

Gross

- Loss of trabecular bone
- Kyphosis of the thoracic spine due to osteoporosis involving more than one vertebral body (dowager sign)

Histology

- Cortical and trabecular bone is decreased with trabecular bone more severely affected
- Bone cortices are thin with widened haversian canals
- Osteoid seams are of normal width
- Trabeculae are thin, discontinuous, and separated

Main differential diagnosis

- Osteogenesis imperfecta
- Malabsorption
- Cushing's syndrome
- Osteomalacia

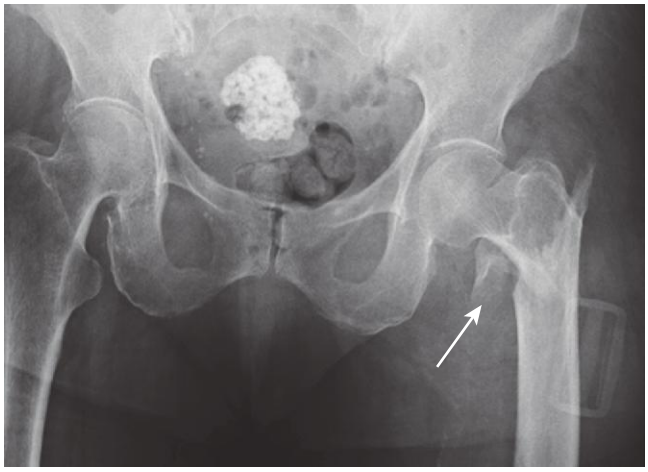


Fig 1. Anteroposterior plain radiograph of the pelvis in a female patient with an osteoporotic intertrochanteric left proximal femur fracture with avulsion of the lesser trochanter (*arrow*). The large calcification in the pelvic soft tissues is a uterine fibroid.

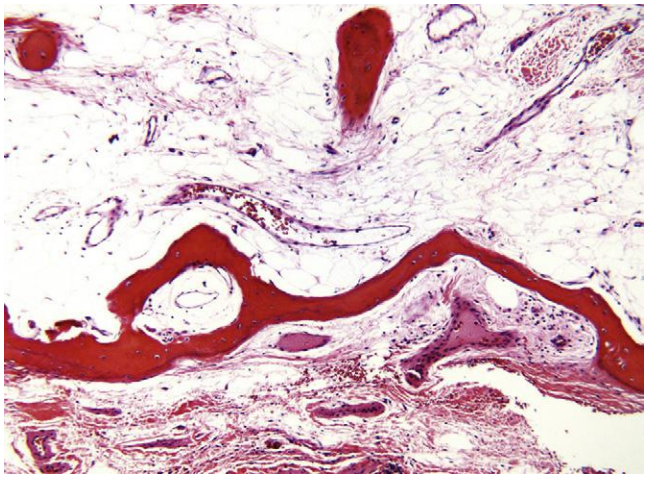


Fig 2. Osteoporotic bone initially affects the trabeculae in the medulla, but this more advanced example shows involvement of the cortex (*bottom*) that is markedly thinned.

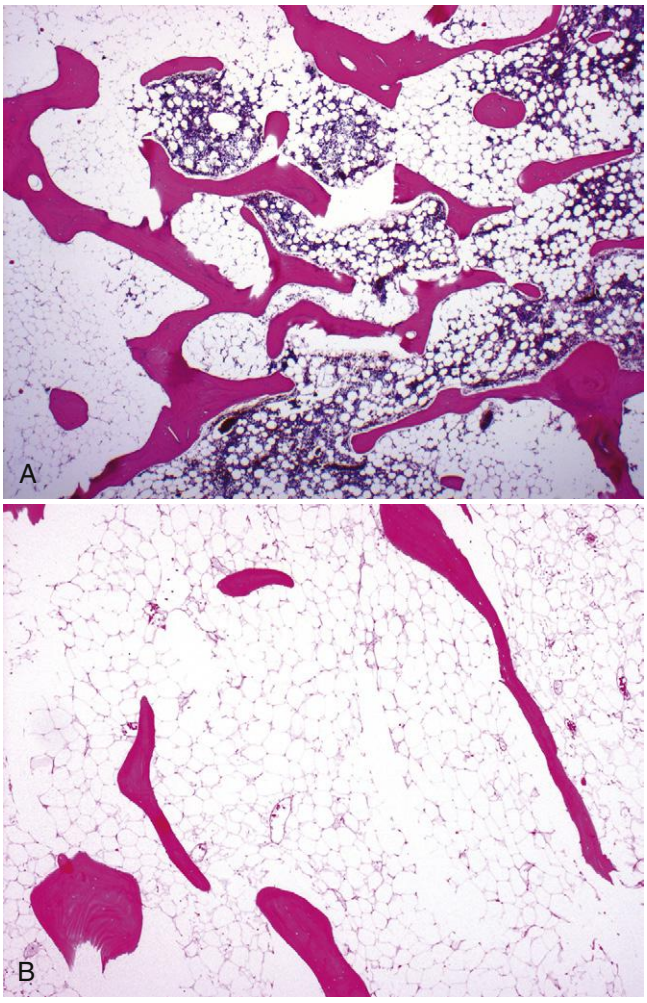


Fig 3. Scanning magnification of normal bone with broad, anastomosing trabeculae (**A**) and bone from a patient with osteoporosis (**B**) showing thin, separated, and discontinuous trabeculae.

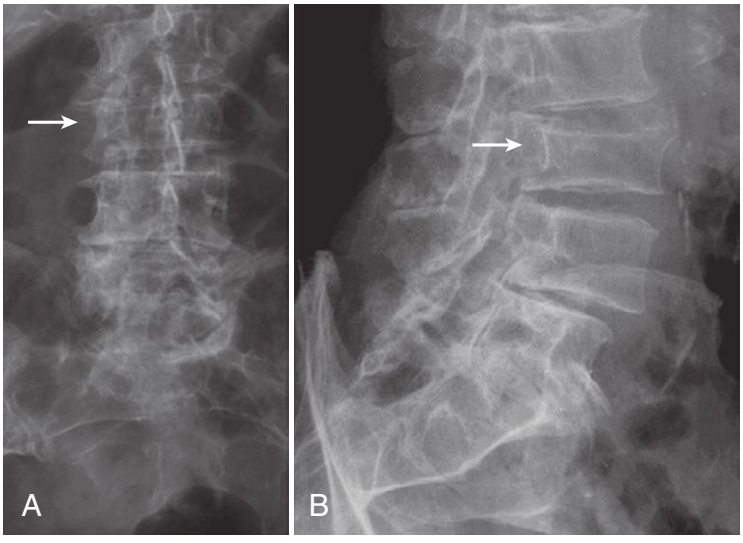


Fig 4. Sequelae of osteoporosis in the lumbar spine. Anteroposterior (**A**) and lateral (**B**) radiographs of the lumbar spine with an osteoporotic fracture of the L3 vertebra (*arrow*) associated with a concave end plate and height loss of the vertebral body.

OSTEOMALACIA

Definition
- General term for a defect in skeletal mineralization that results in the accumulation of unmineralized bone (osteoid); rickets represents defective endochondral ossification at the growth plate resulting in dwarfism (see Osteogenisis Imperfecta, later)

Clinical features
Epidemiology
- Commonly seen in deficiencies or disorders of calcium, vitamin D, or phosphorus metabolism
- Aluminum and iron metal poisoning
- Associated with certain bone and soft tissue tumors (oncogenic osteomalacia), specifically phosphaturic mesenchymal tumor (see Section IIM, Phosphaturic Mesenchymal Tumor)

Presentation
- Generalized musculoskeletal weakness and bone pain
- Fractures with minimal trauma, particularly in vertebral bodies and femoral necks
- Low vitamin D with or without low calcium or low phosphorus levels with high levels of alkaline phosphatase

Prognosis and treatment
- May be a contributing factor to hip fractures in elderly patients
- Treatment is aimed at correcting vitamin deficiencies or underlying medical conditions
- Adequate sunlight exposure and supplemental oral calcium and vitamin D

Radiology
- Symmetrical pseudofractures: unmineralized areas caused by rapid bone resorption and slow mineralization (Looser zones)
- Generalized osteopenia with coarse bone structure
- Multiple bilateral and symmetrical linear insufficiency fractures
- Technetium-99 bone scanning reveals multiple hot spots corresponding to pseudofractures and insufficiency fractures

Pathology
Gross
- Bone particularly from the vertebral column is soft, weak, and prone to fracture easily

Histology
- Bone must be processed without decalcification, and usually embedded in plastic for sectioning
- Increased amount of unmineralized bone or osteoid, surface osteoid greater than 25% (normal is ~2%)
- Increase in osteoid seam thickness, presence of greater than five birefringent lamellar lines in the osteoid seam
- Decreased mineralization or calcification rate
- Tongues of uncalcified cartilage extending into metaphysis

Ancillary studies
- Tetracycline taken before bone biopsy labels sites of new bone formation; a diminished number of osteoid seams taking up tetracycline reflects an absence of mineralization
- Osteoid evaluation can be performed using von Kossa, Goldner, modified trichrome, or Villanueva stain

Main differential diagnosis
- Osteopenia, osteoporosis

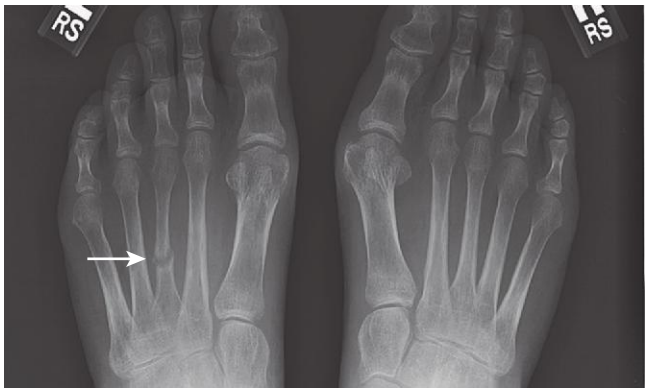


Fig 1. Plain anteroposterior radiographs of bilateral feet in a patient with oncogenic osteomalacia. The bones are severely osteopenic, and a diaphyseal insufficiency fracture is visualized at the left third metatarsal (*arrow*).

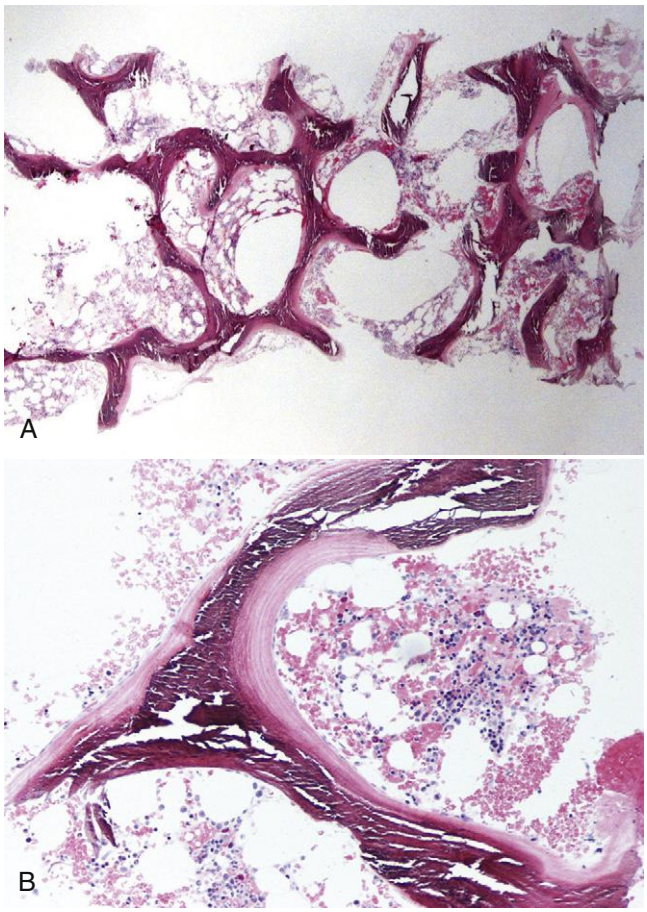


Fig 2. Bone biopsy using von Kossa stain in an undecalcified section with osteomalacia. Osteoid is the eosinophilic unmineralized portion of bone at the surface of trabeculae. The mineralized front is stained dark gray to black (**A** and **B**). Note that a significant fraction of the bone (~50%) is unmineralized. (Courtesy of Roberto Garcia, MD.)

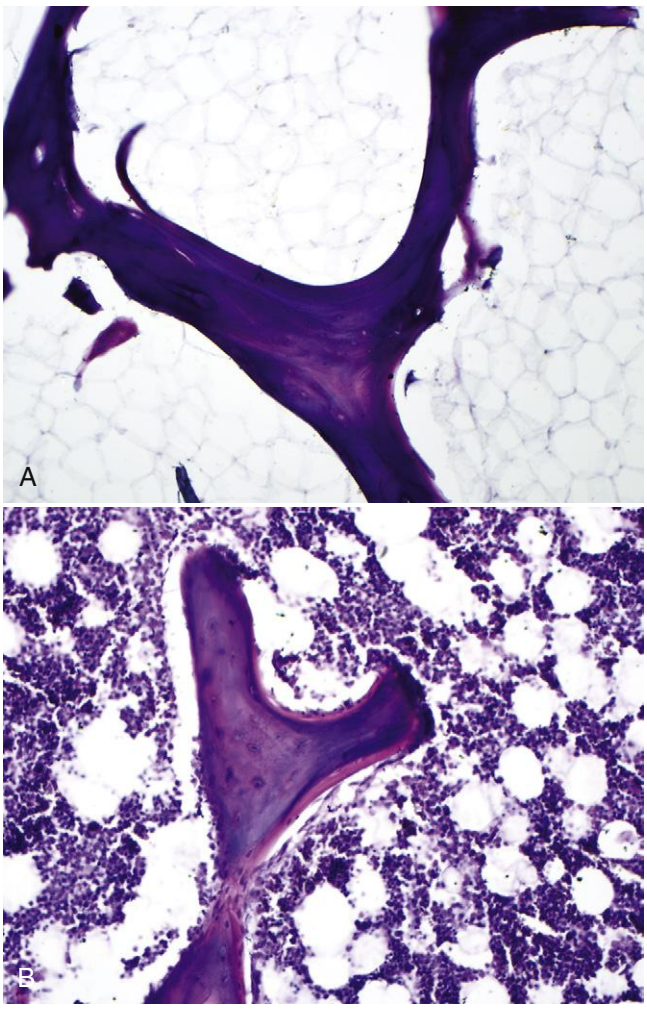


Fig 3. Undecalcified normal bone stained with hematoxylin-eosin (**A** and **B**). Compared with Figure 2, the mineralization front (*purple*) extends essentially up to the surface of the trabeculae, with very little unmineralized osteoid (*pink*).

Definition

- A metabolic bone disorder due to vitamin D, calcium, or phosphate depletion that impairs mineralization of bones in children before growth plate closure, resulting in growth retardation and delayed skeletal development

Clinical features

Epidemiology

- Occurs only in children whose growth plates have not closed, before age 17 years in females and 19 years in males
- Boys and girls are equally affected
- Commonly due to vitamin D deficiency, also from abnormal metabolism of phosphate or gastrointestinal tract disorders
- Hypophosphatasia is a rare X-linked disease characterized by extremely low levels of alkaline phosphatase
- Rare autosomal recessive type I and II vitamin D–dependent rickets (VDDR) due to impaired renal synthesis of 1,25(OH)-D or organ hyporesponsiveness to vitamin D

Presentation

- Clinical findings depend on age of onset and severity of defective mineralization
- Bone pain, tenderness, muscle weakness, fractures, and skeletal deformity are common
- Toddlers present with bowing of the legs; older children present with knock-knees
- Type II VDDR presents in childhood with bone deformity and total-body alopecia

Prognosis and treatment

- No increase in morbidity with adequate treatment
- Prevention of vitamin D deficiency is achieved with adequate sunlight exposure and vitamin D supplementation
- Vitamin D deficiency is treated with ergocalciferol
- Patients with X-linked or idiopathic hypophosphatemia are treated with oral phosphate supplements and calcitriol
- Human recombinant growth hormone reduces phosphaturia
- Type I VDDR is treated with high-dose vitamin D

Radiology

- Plain radiographs show widening and cupping of the metaphyseal region, widening of the growth plate, and fraying of the metaphysis
- Bowing of long bones
- Knock-knees (genu valgum)
- Beading of the ribs at the costochondral junctions ("rachitic rosary")
- Symmetrical and linear pseudofractures (Looser zones)
- Early disease is radiographically difficult to diagnose with nonspecific findings (e.g., osteopenia)

Pathology

Gross

- Frontal bossing of skull, chest deformation, anterior protrusion of the sternum (pigeon breast deformity), kyphosis, scoliosis, and narrowing of the pelvis

Histology

- Wide osteoid seams due to excess osteoid
- Failure of mineralization of the epiphyseal growth plate
- Disordered endochondral ossification with persistence of cartilage growth plate penetrating into medullary cavity

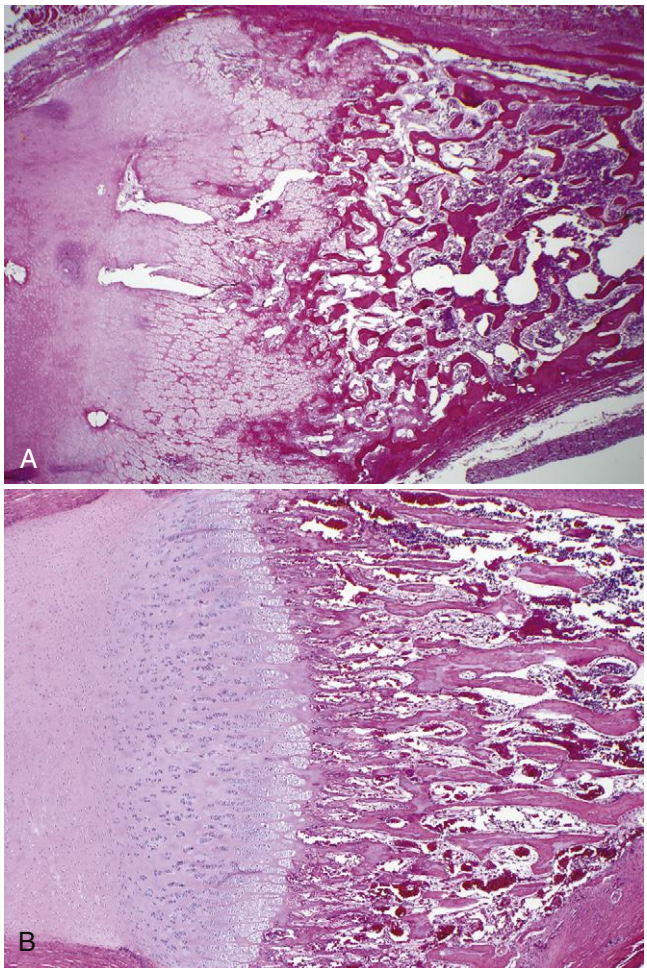


Fig 1. **A,** In this term infant with rickets, disorganized growth plate with cartilage penetrating into the medulla is seen at scanning magnification. **B,** By comparison, a normal growth plate has a sharp line of ossification replacing the cartilage of the growth plate.

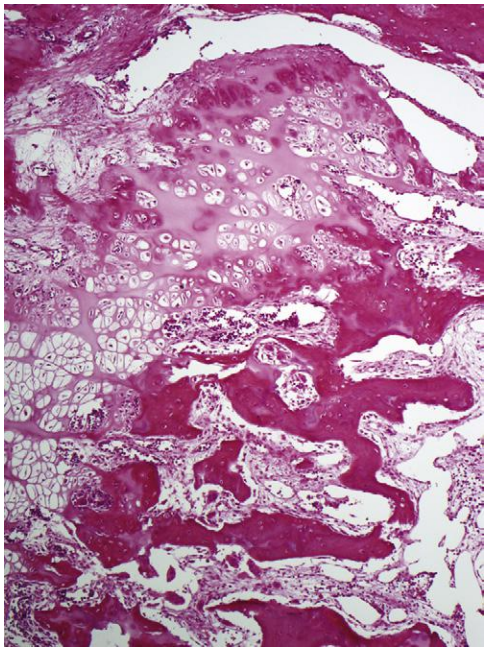


Fig 2. Higher magnification demonstrates marked disorganization of the growth plate with haphazard mixture of hypertrophic zone of chondrocytes and bone in this infant with rickets.

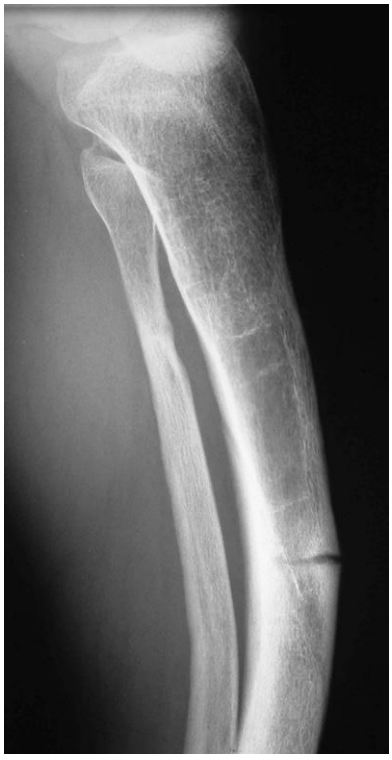


Fig 3. Lateral radiograph of the tibia and fibula in a patient with rickets demonstrating bowing of the tibia and fibula as well as a pseudofracture at the tibia (Looser zone). Coarse trabecular bone structure in the proximal tibia, which is typical of osteomalacia and rickets, is shown.

OSTEOGENESIS IMPERFECTA

Definition and synonyms
- A family of genetic bone disorders primarily due to defective synthesis and secretion of collagen type I, characterized by fragile bones that break easily (brittle bone disease, Lobstein disease).

Clinical features
Epidemiology
- Rare heritable connective tissue disorder with most cases caused by a dominant mutation of type 1 collagen (*COL1A1* or *COL1A2*) genes
- Approximately 35% of patients with OI have no family history
- Type V through type VIII do not involve deficits in type I collagen genes
- Fibrogenesis imperfecta ossium is an extremely rare acquired disorder in which normal bone is replaced by a collagen-deficient tissue that is excessively fragile

Presentation
- Flattened skull, scoliosis, and kyphotic collapsing deformities
- Discoloration of sclera
- Conductive and sensorineural hearing loss
- Small, misshapen, translucent gray-yellow teeth, with enamel that fractures easily (dentinogenesis imperfecta)
- Presentation varies depending on the type of OI inherited
  - Type I: mild bone fragility, rib deformities, blue sclerae
  - Type II: perinatal lethal
  - Type III: progressive severe deformities, fractures, short stature
  - Types IV to VII: moderate growth retardation, deformities
  - Type VIII: severe growth deficiency, normal sclerae

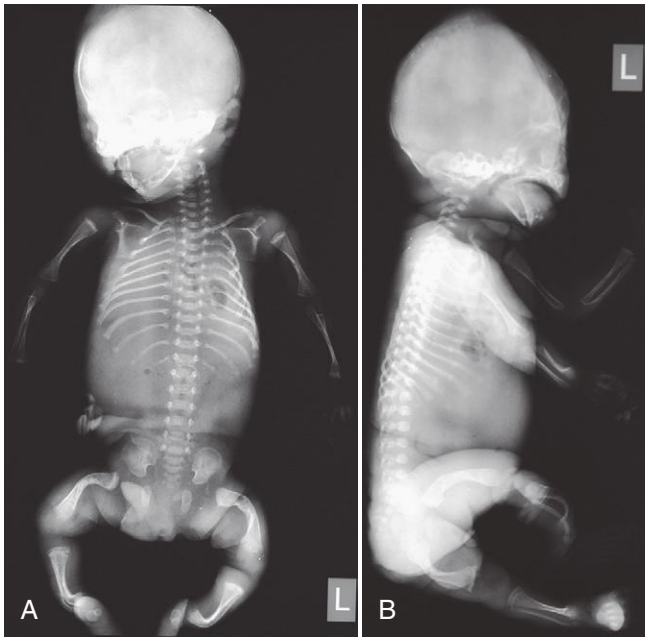


Fig 1. Anteroposterior (**A**) and lateral (**B**) radiographs of a fetus at 32 weeks' gestation with osteogenesis imperfecta type II. Bones show diffuse demineralization and limited calvarial mineralization. Limbs are severely malformed with very short, broad femurs and marked bowing of the tibiae and fibulae.

Prognosis and treatment
- No cure currently; treatment directed toward preventing and controlling symptoms and maximizing independence
- Bisphosphonates improve bone strength
- Percutaneous surgical pinning of fractures and surgical insertion of metal rods through long bones
- Type II usually perinatal lethal

Radiology
- Marked osteoporosis with severe thinning of cortical bone, multiple fractures, and nonunion of healed fractures
- Severe bony deformities
- Diaphysis is thin and wavy; metaphysis is expanded
- Calcified cartilaginous nodules at the growth plates look like popcorn on conventional radiographs

Pathology
Gross
- Biopsy rarely done on lesions
- Fetal cases may be seen at autopsy
- Widened and irregular growth plates
- Cartilaginous nodules at growth plates

Histology
- Severe forms have increased osteocytes, absence of an organized trabecular pattern, and large areas of woven bone
- Bone trabeculae are thin, delicate, and widely separated
- Less severe forms have increased osteocytes with thin lamellar bone

Main differential diagnosis
- Child abuse
- Vitamin D deficiency

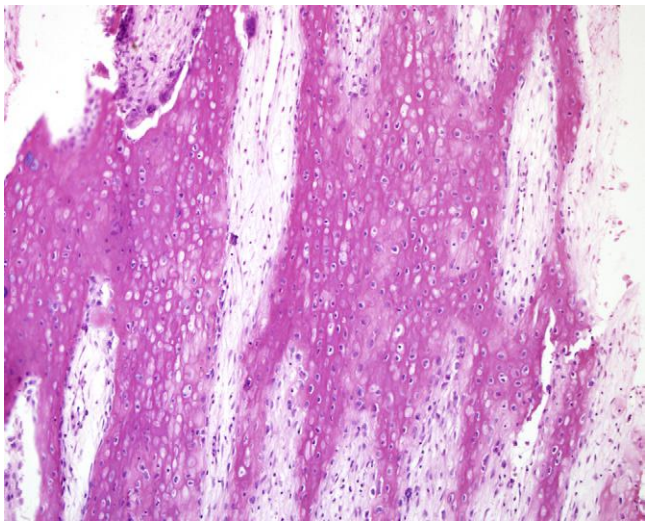


Fig 2. The bone is hypercellular with increased osteocytes in osteogenesis imperfecta.