Chapter 3
General Principles of Bone Pathology

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Bone tumors are among the rarest neoplasms in humans. They account for about 0.8–1 % of all malignancies arising in the body. If we consider that more than 40 bone malignant neoplasms have been described, it is reasonable to think that only large specialized centers may have enough experience with some of them. The peculiar multidisciplinary approach is mandatory in bone tumors, in order to avoid dramatic mistakes. The pathologist dealing with bone must follow a diagnostic flowchart that starts from the accurate collection of clinical information, followed by the careful examination of the imaging, then the decision about the kind of diagnostic procedure to apply, and finally the histological diagnosis. All these steps must be shared with colleagues of the team, the orthopedic surgeons, the radiologists, and the oncologists that will establish the proper treatment after diagnosis. In the last years, pathologists have started to collect biologic samples of fresh tumor tissue to store in biobanks that are necessary for the study of these rare tumors, because of the possibility to perform molecular analyses and to share tissue samples with other institutions in the context of large international scientific projects. Examining in detail every single step of the diagnostic approach, analysis of clinical features, such as patient age, symptoms, and anatomic location of the lesion, is necessary for a preliminary assessment of the lesion. Bone tumors like Ewing sarcoma and osteosarcoma usually occur in young patients. Tumors like chordoma, myeloma, and chondrosarcoma are typical of adults or elderly patients. When osteosarcomas occur in patients older than 50, they are frequently secondary to preexisting bone conditions, such as Paget's disease and bone infarcts, or arising after radiation therapy. Symptoms and features are frequently of great clue for diagnosis. Pain during the night that can be treated with salicylates is typical of osteoid osteoma; the presence of fever favors for the diagnosis of Ewing sarcoma rather than lymphoma.

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An accurate collection of clinical information is mandatory for detection of a primary tumor in case of metastasis to the bone; the blood levels of parathormone are the key feature for diagnosis of hyperparathyroidism. The site of the tumor within the bone and the specific bone segment are very important. Some tumors occur usually in the epiphysis, such as giant cell tumor, chondroblastoma, and clear cell chondrosarcoma; most tumors are centrally located, while others are eccentrically located in the bone cortex; others, such as adamantinoma, occur almost exclusively in the tibial diaphysis. In low-grade chondroid lesions, the site of the lesion is very important for a correct interpretation of histology: if the lesion is in the small bones of the hands and feet, it is usually benign, while, with the same histological features, it is usually malignant if located in the ribs and sternum. Lesions that arise in the periosteum are generally clinically less aggressive than the medullary counterparts. The radiographic features of the lesion as well are very important for the pathologist: they have to be considered like a negative image of the macroscopic appearance of the neoplasm. Bone lesions can cause osteolysis or reactive bone production (osteosclerosis). Combinations of these two processes give three typical patterns of bone destruction:

1. The geographic bone destruction pattern, typical of slow-growing lesions.
2. The "moth-eaten" pattern that is typical of more aggressive lesions that usually have a faster growth rate, and for this reason the osteosclerosis in this situation is less evident.
3. The permeative growth that can be observed in the most aggressive lesions, such as lymphomas and Ewing sarcoma.

Finally, periosteal reaction gives a great clue for interpretation of biological features of a bone neoplasm. Fast-growing lesions do not cause a periosteal reaction that usually requires about 2 weeks to be detectable on radiographs. Some kinds of periosteal reactions suggest a specific diagnosis (onionskin reaction is frequently present in Ewing sarcoma). After a careful examination of all these aspects, the pathologist can correctly interpret the histology of a given bone lesion.

From a histological point of view, the 2013 WHO classification of bone tumors is based on cytologic and histogenetic criteria and on the kind of matrix produced by the tumor. Table 4.1 represents the classification used today. Bone-producing lesions, together with cartilaginous lesions and Ewing sarcoma, account for about 80 % of all bone tumors; the remaining entities are by far rarer and all together account for about 20 %. The use of ancillary techniques, such as immunohistochemistry, is very important for the assessment of the possible origin of a bone metastasis but also in some primary bone tumors (i.e., chordoma and adamantinoma). Molecular techniques have some technical limitations that are due to the use of decalcifying solutions in bone tumors but are widely used in the validation of the diagnosis of Ewing sarcoma and in other situations always more frequently described (primary aneurysmal bone cyst, fibrous dysplasia). The grading system for bone sarcomas used at the Rizzoli Institute is a four-grading system according to Broders (grades 1–2, low grade; grades 3–4, high grade).

The Rizzoli's syllabus is based on the study of the most numerically important series in the world, and the use of a schematic approach for every single entity gives the reader a useful diagnostic tool, very practical for such rare diseases.

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