Chapter 2
Bone/Osteoid Producing Lesions

INTRODUCTION
There are many lesions that are associated with reactive new bone formation; this chapter predominantly covers those in which deposition of osteoid/bone matrix represents the primary pathological process. The key in recognizing these lesions is the identification of osteoid or woven bone (vs. lamellar bone) on the frozen section slide. Osteoid is the organic nonmineralized matrix of bone and, being predominantly composed of type I collagen fibers, appears homogeneously eosinophilic and almost keloid-like in nature. This matrix is almost always associated with osteoblasts within clear spaces or halos. Bone matrix is further classified as lamellar or woven depending upon the predominant fiber arrangement of its collagen. In lamellar bone, the bone collagen fibers are arranged in tightly packed stacks that are parallel to one another but run at slightly different angles so that the bone appears to be layered. Moreover, the osteoblasts/osteocytes within lamellar bone also run parallel to the collagen fibers. After about 3 years of age, normal compact (cortical) and cancellous (trabecular, spongy, and medullary) bone exclusively consist of lamellar bone. In contrast, woven bone is found in the fetal skeleton, in the growing parts of the skeleton in infants and adolescents, and in processes in which there is very rapid bone production secondary to neoplastic or nonneoplastic conditions. Accordingly, identification of lesional woven bone and its distinction from adjacent lamellar bone is crucial during frozen section evaluation. This is based on the fact that, in contrast to lamellar bone, woven bone is characterized by the random distribution of its collagen fibers and the irregular distribution of osteoblasts within it. Although the distinction between
lamellar and woven bone can, for the most part, be made using regular bright-field microscopy, the process can be facilitated with the use of polarized light.

Once the presence of bone matrix has been established, one has to determine if its presence is primary or secondary in nature, a determination often compounded by the fact that many frozen section samples include intermixed curettings from the lamellar bone immediately adjacent to the lesion in question. In most cases, where the production of new bone is secondary, its presence tends to be focal in nature and closely intermixed with other reactive elements including hemorrhage and osteoclast giant cells. Moreover, there is usually a zonal distribution which may not be easily appreciated in curetting specimens. On the other hand, bone production in most cases of primary bone-producing lesions tends to more extensive and generally not intimately associated with reactive elements, that, if present, also tend to be peripherally located.

As stated throughout this book, evaluation of any bone lesion (intraoperatively or otherwise) should not be made independently from the clinical (age of the patient, bone involved, and portion of bone involved) and radiological findings. This is no less true for the bone-producing lesions discussed in this chapter, which, although having overlapping histological features, can have quite distinct clinical and/or radiological features that are crucial to arriving at the correct diagnosis.

**FRACTURE CALLUS**

Although fractures are numerically one of the most frequent bone “disorders,” intraoperative consultation is infrequently requested unless the fracture is thought to be pathological in nature. Although acute fractures can be hemorrhagic and display some fragmented bone trabeculae, these changes are nonspecific and are very difficult to evaluate in the setting of the artifacts associated with frozen sections. Subacute fractures (meaning a few days old, rather than hours or weeks) may also display empty osteocyte lacunae and necrosis of marrow. Older fractures that do not readily heal and, as noted above, those that are thought to be pathologic, are more frequently sampled to rule out the presence of an occult neoplasm or infection. In the absence of these etiologies mimicking the natural healing process that moves from fibrosis to chondrogenesis to osteogenesis in long bones, one observes irregular islands and trabeculae of osteoid with an intervening, variably cellular reactive spindle-cell stroma. Scattered osteoclasts are frequently present (Figs. 2.1 and 2.2) as are islands of cartilage (Fig. 2.3). It is very important to know that there is a history of trauma, otherwise
Figure 2.1  Low power view of a fracture callus showing a cellular infiltrate in which scattered eosinophilic islands of osteoid are evident.

Figure 2.2  On higher magnification, this fracture callus shows a predominantly spindle-cell component in which scattered osteoclasts are evident. Notice that although the osteoid islands are mostly irregular in shape, one starts to appreciate the somewhat parallel alignment of these islands (running downwards and to the right in this field). Such an appearance is strongly in favor of reactive, nonneoplastic osteoid deposition.
one might misinterpret the osteoid as being neoplastic in nature. Of note, primary bone-producing neoplasms are rarely the sites of fracture unless radiographically evident and quite large.

There are a few histological parameters that help to distinguish bone (and cartilage) formation by tumor from that secondary to trauma; however, it might be difficult to appreciate

**Figure 2.3** Hyaline cartilage is frequently a component of fracture callus (a). The presence of orderly endochondral ossification (b) is another helpful feature of benignity.
them in frozen sections. Although reactive osteoid may start off focally lacelike in appearance (Fig. 2.4), it rapidly acquires a microtrabecular to trabecular architecture as it matures, and there is almost always a zonation of orderly maturation (Fig. 2.5).

**Figure 2.4** The presence of focal lace-like areas of osteoid deposition in a fracture callus can be worrisome for neoplasia. However, this focus also displays an edematous spindle-cell stroma with scattered inflammatory cells and osteoclasts and no evidence of cytological atypia.
In contrast, neoplastic osteoid invariably has a lace-like or sheet-like appearance (see below) and there is no orderly maturation.

**REACTIVE BONE**

In addition to being a component of fracture callus, as noted earlier, reactive bone may be seen accompanying a variety of bone infections with secondary attempts at healing/repair. As such, this often surrounds the lesion in question or is part of an accompanying reactive periosteal new bone formation. The orderly parallel arrangement of the trabeculae/microtrabeculae in reactive bone (Fig. 2.6) is characteristic.

**OSTEOMA**

The characteristic clinical and radiographic findings of this benign lesion, when linked to its classic location in the skull and sinuses, make it an unlikely frozen section sample. Moreover, its dense bony nature would make sectioning virtually impossible.

**OSTEOID OSTEOMA**

This bone-forming tumor is relatively common, representing at least 10% of all benign bone neoplasms. Most patients are between 10 and 30 years of age and the lesion most frequently involves the cortex of long bones. One of osteoid osteoma’s characteristic
symptoms is progressive pain, easily relieved by ingestion of nonsteroidal anti-inflammatory drugs. Radiologically, a radiolucent “nidus” surrounded by sclerotic bone is quite characteristic (Fig. 2.7). Histologically, the nidus is composed of vascularized fibroconnective tissue in which osteoid or mineralized new bone is evident. This new bone is usually arranged in microtrabecular arrays, lined by plump appositional osteoblasts, and surrounded by sclerotic bone. Given its characteristic clinical and radiological features, osteoid osteoma is rarely sampled intraoperatively. Moreover, definitive treatment by radiofrequency ablation or cryotherapy is not infrequently performed prior to pathological confirmation of the diagnosis. Unfortunately, in most of these cases, one sees only markedly fragmented nonviable bone (sometimes referred to as “bone dust”) that is nondiagnostic histologically.

Osteoblastoma
The histological features of this neoplasm are identical to those of osteoid osteoma except for the fact that it has an expanded growth potential. It also arises in adolescence and young adulthood and frequently involves the cortices of long bones; however, spinal vertebrae are also a common site of involvement (Fig. 2.8). As noted above, microtrabecular arrays of osteoid or woven bone lined by plump osteoblasts dominate the histological appearance (Fig. 2.9). Some cases can be significantly more cellular being composed of
Figure 2.7 An osteoid osteoma of the humerus showing the characteristic lucent nidus (arrow) surrounded by sclerotic bone.

Figure 2.8 An osteoblastoma appearing on plain radiograph (a) as an expansile lesion in the transverse process of the third lumbar vertebra (arrows). The expansile nature of the lesion is also quite apparent on the CT scan (b) (images courtesy of Dr. Michael J. Klein, Hospital for Special Surgery, New York, NY).
sheets of tumor cells with less easily discernable osteoid (Fig. 2.10). Lack of nuclear pleomorphism in the conventional forms of this neoplasm is one feature that is useful to distinguish them from other variants including the “aggressive” and “epithelioid” types. Pathologists need to be aware that there is a histologic continuum between conventional osteoblastoma and osteosarcoma, with the osteoblastoma variants in the middle. Considering the histological (and radiological) difficulty in recognizing these variants and distinguishing them from osteosarcoma, it is prudent to defer the diagnosis of atypical cases to permanent sections.

**OSTEOSARcoma**

Excluding hematopoietic tumors, osteosarcoma is the most common primary malignant neoplasm of bone. The peak incidence is late childhood and adolescence, but there is another peak in patients over 50 years where most cases develop secondarily in preexisting bone lesions, such as Paget’s disease or following irradiation. The metaphyses of long bones (femur, tibia, and humerus) are the most common sites of involvement, isolated diaphysial involvement is rare, while involvement of the epiphyses of long bones or small bones of the hands and feet is exceptionally uncommon. The tumor may also involve the jaws, skull and axial skeleton. A significant proportion of patients presents with pain (often dull and unremitting) with or without a palpable mass. Radiologically, there is almost always evidence of a destructive bony lesion, often with evidence of new bone formation. There may also be an interrupted periosteal reaction (Fig. 2.11).
The histological hallmark of osteosarcoma is the presence of tumor osteoid or bone being formed directly by tumor cells. Similar to that seen in fracture callus and osteoblastoma, tumor osteoid has unique tinctorial properties on hematoxylin and eosin-stained sections appearing as dense, pink, amorphous material that is often described as “hard.” As noted above, osteoid may have a lace-like (Fig. 2.12) or sheet-like (Fig. 2.13) appearance in osteosarcomas. Although subclassification of osteosarcomas as osteoblastic, chondroblastic, or fibroblastic based upon the predominant matrix produced has no prognostic impact, identification of a significant...
chondroid or spindle-cell component independent of the osteoid matrix may also be a useful clue toward the diagnosis. The neoplastic tumor cells are usually seen intermixed within the osteoid matrix but occasionally may appear to be in direct opposition to it; they may even be condensed around it in a palisaded fashion.

Figure 2.10 This osteoblastoma was markedly cellular (a) to the extent that osteoid could only be focally identified (arrowheads). Higher magnification (b) confirms the hypercellular nature of the neoplasm and better displays the osteoid matrix. One should always remember that nuclear atypia is exaggerated on frozen sections and thus be careful not to make a diagnosis of osteosarcoma based solely on that feature.
Morphologically, the tumor cells are usually round to polyhedral in shape and significant pleomorphism is usually present (Figs. 2.12 and 2.14). In other cases, the tumor cells can have a predominantly spindle-cell morphology (Fig. 2.15). It is important to note, however, that significant nuclear atypia may not always be present in conventional high-grade lesions, in that case
the radiological evidence of a destructive bony lesion can be one of the most useful clues to suggest the diagnosis of osteosarcoma.

In addition to conventional intramedullary osteosarcoma, the prototypical central osteosarcoma discussed above, there are other variants of osteosarcoma, including some that are potentially more challenging diagnostically.
Low-grade central osteosarcoma is composed of a variably cellular spindle-cell/fibroblastic proliferation that, as the name suggests, lacks the degree of cytological atypia seen in conventional osteosarcoma. Moreover, bone production within this spindle-cell proliferation appears as irregular, somewhat thick, anastomosing or branching bony trabeculae that simulate the
woven bone of fibrous dysplasia, or the longitudinal seams of bone seen in parosteal osteosarcoma (see below). Although review of the radiological findings often reveals subtle signs of malignancy and helps to exclude a benign lesion such as fibrous dysplasia or desmoplastic fibroma, it is best to defer the diagnosis of this rare variant to the permanent sections.

_Telangiectatic osteosarcoma_ is characterized by large blood-filled spaces separated by hypercellular fibrous septae that contain

**Figure 2.14** Hyperchromasia and nuclear atypia can be appreciated in this osteosarcoma, even at this low power.
variable amounts of tumor osteoid and markedly pleomorphic cells. Although one might not readily see the osteoid on a single frozen section slide, the degree of pleomorphism present in the cells lining the blood lakes usually makes the diagnosis of malignancy relatively straightforward. This, along with the tumor's characteristic radiolucent and expansile appearance on radiological examination, should strongly suggest the diagnosis.
Small cell osteosarcoma histologically resembles Ewing’s sarcoma, except that there is at least focal evidence (usually scant) of osteoid formation (Fig. 2.16).

In contrast to central osteosarcomas that arise in the medullary cavity, the much less common surface osteosarcomas arise on the
cortical surface. Of these, *high-grade surface osteosarcoma* is histologically identical to conventional intramedullary osteosarcoma; *parosteal osteosarcoma* (the commonest surface osteosarcoma) resembles low-grade central osteosarcoma, whereas periosteal osteosarcoma characteristically has abundant cartilaginous matrix and cytomorphologically falls between the low- and high-grade variants.

Again, it should be stressed that although awareness of the particular features of the osteosarcoma variants is useful especially to avoid a misdiagnosis, subclassification of osteosarcoma is seldom necessary on frozen section interpretation and is best deferred to permanent sections.
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