Tumors of the Pelvis: Pathologic Aspect

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4.1 Introduction

Tumors of the pelvis are histologically similar to tumors arising in the extremities; however, less than 5% of primary sarcomas are found in the pelvis. Since patients with pelvic tumors often present with nonspecific symptoms, the diagnosis can be delayed, allowing these tumors to get quite large. Due to their size and relationship to other visceral structures, the surgical margins which are able to be achieved at the time of surgery are considered marginal, and disease recurrence is a problem. In order to formulate a treatment plan, and to have an educated discussion with patients on treatment outcome, an accurate diagnosis is needed. Imaging studies can narrow the differential diagnosis; however, a tissue diagnosis is imperative for treatment planning. The purpose of this chapter is to provide a general pathology review of some of the common tumors of the pelvis.

4.2 Soft Tissue Sarcomas

Primary soft tissue sarcomas of the pelvis are rare, with a majority originating from genitourinary system [1, 2]. These tumors are often large at the time of presentation and considered high grade with extra-compartmental extension, making it difficult to obtain a wide surgical margin, often making them a lethal disease [1, 3]. Liposarcoma and leiomyosarcoma represent the most common sarcomas of the abdomen and pelvis.

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4.2.1 Liposarcoma

Adipocytic tumors are frequently encountered by surgeons and pathologists, the majority of which are benign. Lipomas are the most common mesenchymal neoplasm in adults, but it rarely occurs in the retroperitoneum [4]. There are four types of liposarcoma including well-differentiated, myxoid, pleomorphic, and dedifferentiated liposarcoma. These tumors are typically low and intermediate grade; however, negative predictive factors for recurrence include poorly differentiated tumors, grade and stage 2 or 3 tumors, those larger than 20 cm, and a positive margin [5]. Liposarcomas are the most common retroperitoneal tumor in adults, but they can also be found in the true pelvis [6]. These tumors often present as a large mass, and often patients with retroperitoneal liposarcomas are older than patients with extremity tumors.

Well-differentiated liposarcoma (Fig. 4.1), which is synonymously called atypical lipomatous tumor (ALT) when located outside the body cavities, is the most common type of liposarcoma in the retroperitoneum. These tumors do not metastasize but may progress into a non-lipomatous form referred to as dedifferentiated liposarcoma. Well-differentiated liposarcomas are subdivided into three main histologic subtypes including adipocytic (lipoma-like), sclerosing, and inflammatory [7]. The presence of more than one histologic pattern in a single tumor is common, particularly in the retroperitoneum. The diagnosis is based on identifying adipocytes with varying degrees of cytologic atypia, often found within fibrous septa coursing throughout the tumor, in the background of mature fat. Most well-differentiated/ALT tumors can be diagnosed by histologic criteria, but at times the diagnosis can be challenging because areas of atypia can be focal. When faced with equivocal or borderline atypia, pathologists often rely on fluorescence in situ hybridization (FISH) testing for *MDM2* gene amplification, a consistent finding in well-differentiated liposarcoma/ALT [8, 9]. Moreover, FISH has

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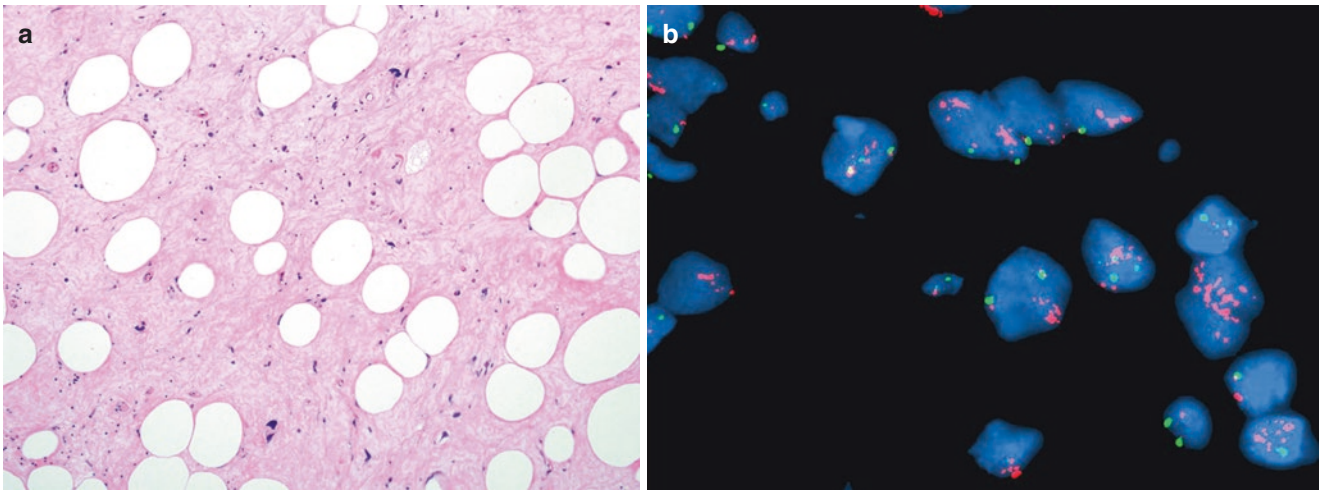

Fig. 4.1 Well-differentiated liposarcoma (sclerosing variant) demonstrating adipocytic cells embedded in a fibrillary collagenous background containing scattered atypical, hyperchromatic tumor cells (**a**). Fluorescence in situ hybridization (FISH) study illustrating *MDM2* amplification (**b**), a characteristic feature of atypical lipomatous tumor (ALT)/well-differentiated liposarcoma

been found to be a more reliable and cost-effective method when compared to immunohistochemical staining for *MDM2* and/or CDK4 [10]. In terms of treatment, patients with a sclerosing variant of well-differentiated liposarcomas, as well as those with positive surgical margins, are more likely to develop local recurrence [9].

Dedifferentiation occurs in approximately 10% of well-differentiated liposarcomas, although the risk is higher for those in the retroperitoneum where the majority of dedifferentiated liposarcomas occur. Histologically, most dedifferentiated liposarcomas are composed of a well-differentiated component and a high-grade non-lipogenic component most frequently resembling an undifferentiated pleomorphic sarcoma. These tumors may be misdiagnosed as the histologic subtype of the high-grade area due to inadequate sampling of a resected tumor or limited biopsy tissue. Dedifferentiated liposarcoma is characterized by a high incidence of local recurrence, and distant metastases arise in up to 18% of patients [11]. Occasionally, the areas of dedifferentiation are low grade, creating difficulties in the distinction from well-differentiated liposarcoma.

Myxoid liposarcoma occurs almost exclusively in the extremities in young adults. Genetically, it is characterized by the presence of *FUS-DDIT3* (>90%) or *EWSR1-DDIT3* (<10%) fusion genes. Myxoid liposarcoma is extremely rare in the retroperitoneum and usually represents metastatic tumor in this location [12]. Histologically, the tumor is composed of a myxoid stroma containing ovoid to round cells and prominent capillaries. Areas with myxoid features in well-differentiated liposarcoma may be confused with myxoid liposarcoma.

Pleomorphic liposarcoma is the rarest type of liposarcoma, accounting for 5% of all liposarcomas, and it carries a worse prognosis [13–15]. These tumors are high-grade pleomorphic sarcomas with multivacuolated lipoblasts with hyperchromatic scalloped nuclei and concave indentations created by clear cytoplasmic vacuoles [16, 17]. Compared to other liposarcomas, these are aggressive tumors with a reported 5-year survival of 63%, and as such an aggressive multidisciplinary care team is recommended [13].

4.2.2 Leiomyosarcoma

Leiomyosarcoma is the second most common soft tissue sarcoma of the retroperitoneum and typically presents as a large, nonfatty mass with the ability to extend into the surrounding vascular structures, specifically the inferior vena cava [18]. Histologically, leiomyosarcomas are typically composed of elongated spindled cells with blunt-ended nuclei arranged in intersecting fascicles. Epithelioid cytomorphology, myxoid change, and osteoclast-type giant cells are occasional findings. Poorly differentiated high-grade tumors may resemble other types of pleomorphic sarcomas. Immunohistochemical stains are often helpful in making the diagnosis. Smooth muscle actin and h-caldesmon are positive in >70% of leiomyosarcomas [19].

Previous studies have focused on the tumor depth and size, grade, mitotic rate, and presence of vascular invasion as to determine the prognosis of survival [19, 20]. In addition to these factors, it has also been shown that the location of the tumor plays an important factor in disease recurrence and can behave differently based on the anatomical site. Compared to patients with tumors of the extremity, those with tumors of the pelvis have worse overall survival [21].

4.3 Primary Bone Sarcomas

Treatment of malignant bone tumors of the pelvis is difficult due to the local anatomy, poor compartmentalization of the pelvis, and ability to achieve a wide surgical margin [22, 23]. In the pelvis, chondrosarcoma, Ewing sarcoma, and osteosarcoma are frequently encountered with the ability to achieve a negative surgical margin, the best predictor to prevent local recurrence and improve survival [22, 24].

4.3.1 Chondrosarcoma

Chondrosarcoma is the most common primary malignancy of the bones of the pelvis. The preliminary diagnosis of these tumors is often based on the clinical and radiographic features of the tumor; however, the pathologic findings confirm the diagnosis. Similar to the extremities, chondrosarcomas can be a primary bone tumor or a secondary tumor arising in patients with Ollier disease or an osteochondroma.

Histologically, chondrosarcomas show an infiltrative growth pattern characterized by tumor encasing preexisting trabecular bone (Fig. 4.2), the single most important finding that distinguishes it from enchondroma. Chondrosarcomas contain increased cellularity, nuclear enlargement/hyperchromasia, and myxoid matrix which become more prominent with increasing histologic grade (1 to 3). Dedifferentiated chondrosarcoma is a biphasic tumor, with areas of low-grade chondrosarcoma adjacent to a high-grade sarcoma, usually undifferentiated pleomorphic sarcoma. The diagnosis may be missed if inadequate tissue sampling fails to provide tissue from both components. Radiologic correlation can be helpful in avoiding this problem. In terms of treatment outcome, the grade of the tumor has been found to be one of the most important features for disease-specific and overall survival, with patients with higher-grade tumors (3 or dedifferentiated) having increased mortality compared to patients with lower-grade tumors (1 or 2) [25, 26].

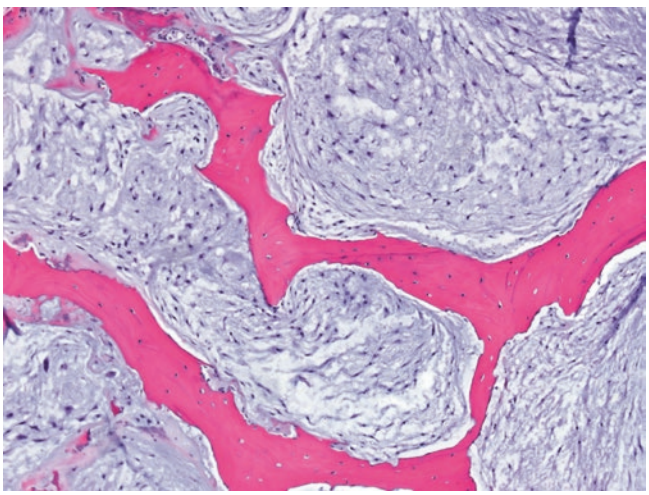

Fig. 4.2 Representative section of a chondrosarcoma showing a malignant hyaline cartilage tumor with increased cellularity and myxoid change in the matrix. The tumor is encasing the preexisting cancellous bone

The diagnosis of enchondroma involving a pelvic bone should be made with great caution as the vast majority of hyaline cartilage tumors in this location are at least low-grade malignant. On core needle biopsy tissue, it may be impossible to differentiate between enchondroma and low-grade chondrosarcoma at any anatomical site. In this situation, pathology can confirm the presence of a hyaline cartilage tumor which is then correlated with the radiologic features. The histologic differential diagnosis primarily includes chondroblastic osteosarcoma. In general, the cartilaginous component of chondroblastic osteosarcoma is higher grade than the majority of chondrosarcomas involving the pelvis. Moreover, the presence of malignant osteoid production rules out chondrosarcoma. At times, the distinction may be challenging, particularly with a limited amount of biopsy tissue. In these cases, mutation analysis looking for isocitrate dehydrogenase genes *IDH1* and *IDH2* may be helpful because these genes are mutated in 38–70% of primary chondrosarcomas and 86% of secondary chondrosarcomas [27].

The concordance of the preoperative biopsy and the final pathology for chondrosarcoma has historically been poor, especially in the pelvis [28]. This can potentially lead to treatment errors and is related to the heterogenicity of chondrosarcomas and the small amount of tissue obtained from a needle biopsy. This is especially apparent in the pelvis, where the tumors are often very large. Due to the heterogeneity, it is recommended to use the preoperative MRI to select specific areas with higher-grade features (reduced signal intensity of T2 MRI) to obtain the biopsy; however, even with obtaining tissue from this region, the diagnosis of a high-grade tumor can be missed [28].

4.3.2 Ewing Sarcoma

The most common axial site for Ewing sarcoma is the pelvis, and it is typically observed in pediatric and adolescent patients [29]. Grossly, Ewing sarcoma can have a liquid appearance resembling pus. Histologically, Ewing sarcoma demonstrates sheets or irregular islands of small blue cells containing oval nuclei with finely distributed chromatin surrounded by scant eosinophilic or clear cytoplasm. A small subset of Ewing sarcomas, previously classified as primitive neuroectodermal tumor (PNET), contain Homer Wright rosette formation suggestive of neural differentiation. By immunohistochemistry, the vast majority (90%) express CD99 and FLI-1. Approximately 20% show keratin

positivity, a feature that may result in a mistaken diagnosis of metastatic small cell carcinoma. The histologic features of Ewing sarcoma can mimic hematopoietic neoplasms, particularly lymphoma. However, a thorough panel of immunohistochemical stains should be able to sort through this differential diagnosis. Similar to Ewing sarcoma, *BCOR-CCNB3* and *CIC-DUX4* tumors contain small blue cells and can show patchy CD99 positivity, and the distinction is made by molecular testing [30, 31].

The majority of Ewing sarcomas have a translocation between *EWSR1* and member of the ETS gene family. Most (85%) have t(11:22)(q24;q12), and 5–10% harbor t(21;22)(q2q12). This leads to the expression of the fusion oncogenes *EWS-ETS*, and detection of this gene fusion is used in the diagnosis (*EWS-FLI1* and *EWS-ERG*) [32]. Multi-agent chemotherapy and radiotherapy have improved the survival of patients with extremity Ewing. In the pelvis 5-year survival remains poor [33]; however, it can be improved when combined with appropriate surgical resection with negative margins [34].

4.3.3 Osteosarcoma

Conventional osteosarcoma is the second most common primary malignancy of bone in adults [35]. Secondary osteosarcoma involving the pelvic bones is usually seen in adult patients who have received radiation therapy to the area for a malignancy or in patients with Paget disease. Similar to Ewing sarcoma, unlike extremity osteosarcoma where the use of adjuvant treatments has improved survival, even with aggressive treatments, the reported 5-year overall survival of osteosarcoma of the pelvis is 38% [36]. The management is challenging due to the difficulty in achieving a complete surgical excision with adequate margins.

By definition, conventional osteosarcoma is a high-grade malignancy. Histologically, it is composed of malignant osteoid produced by atypical pleomorphic cells with a high nuclear-to-cytoplasmic ratio. The neoplastic bone usually has a disorganized lacelike appearance, but it can also be deposited in sheets or thick trabeculae. There are a variety of different subtypes, but the most common include chondroblastic, osteoblastic, and fibroblastic osteosarcoma. The radiologic features of osteosarcoma involving the pelvic bones are usually those of a malignant tumor, so the diagnosis is often made on tissue obtained from an image-guided needle biopsy procedure. The tumor cells typically display high-grade malignant features throughout the neoplasm, a feature that aids in making the diagnosis on a limited amount of tissue. However, the amount and distribution of malignant osteoid are variable and may hinder a definitive diagnosis. Immunohistochemical staining for SATB2, a marker for osteogenic differentiation, can be helpful in problematic cases [37]. However, caution is required as SATB2 is not specific for osteosarcoma and can be positive in benign and malignant mesenchymal tumors. Conventional osteosarcoma has complex karyotypes with an abundance of numerical and structural alterations. No specific translocation has been identified that would be helpful as a diagnostic test. Molecular testing for *IDH1* or *IDH2* mutations may be helpful in separating chondrosarcoma from chondroblastic osteosarcoma.

In the pelvis, the most common histologic subtypes are chondroblastic and osteoblastic osteosarcoma, with a high percentage of patients having metastatic disease at the time of presentation [36, 38–40]. In a study at a single institution with similar treatment protocols, the 5-year survival for extremity osteosarcoma was 75%; however, in the pelvis, it was 33% [38]. The authors of the study theorized that the poor chemosensitivity (20% good responders) and the high local recurrence accounted for the poor prognosis of pelvic osteosarcoma [38].

4.3.4 Chordoma

Chordomas are malignant tumors of notochordal origin and the most common malignant neoplasm of the sacrum [41]. Since they are typically slow-growing tumors, they are frequently very large at the time of diagnosis. Grossly, chordomas have a lobulated and gelatinous appearance. Histologically, at low magnification, the tumor has a lobular and infiltrative growth pattern. The tumor cells are arranged in nests and cords within a myxoid stroma (Fig. 4.3). Cytologically, they contain dark round nuclei with a moderate degree of atypia surrounded by eosinophilic cytoplasm. Intracytoplasmic vacuoles are a common feature, and cells containing them are known as physaliphorous cells. The amount of nuclear pleomorphism and necrosis can vary from tumor to tumor; however, this has not been associated with clinical outcome [42]. By immunohistochemistry, the vast majority of chordomas are positive for brachyury, the most sensitive and specific marker for diagnostic purposes. They are also positive for keratin markers, a feature that can be helpful in separating chordoma from other sarcomas, such as chondrosarcoma, but not of use when ruling out carcinoma. Clinically, the main prognostic factor in determining survival was the ability to achieve a wide margin [42].

4.3.4.1 Benign Lesions

Osteochondroma

Osteochondromas are the most common benign bone tumor. They arise on the surface of bones as either a pedunculated or broad-based mass which is in continuity with the cortex and medullary canal of the underlying bone. Histologically, osteochondromas contain a peripheral cartilaginous cap

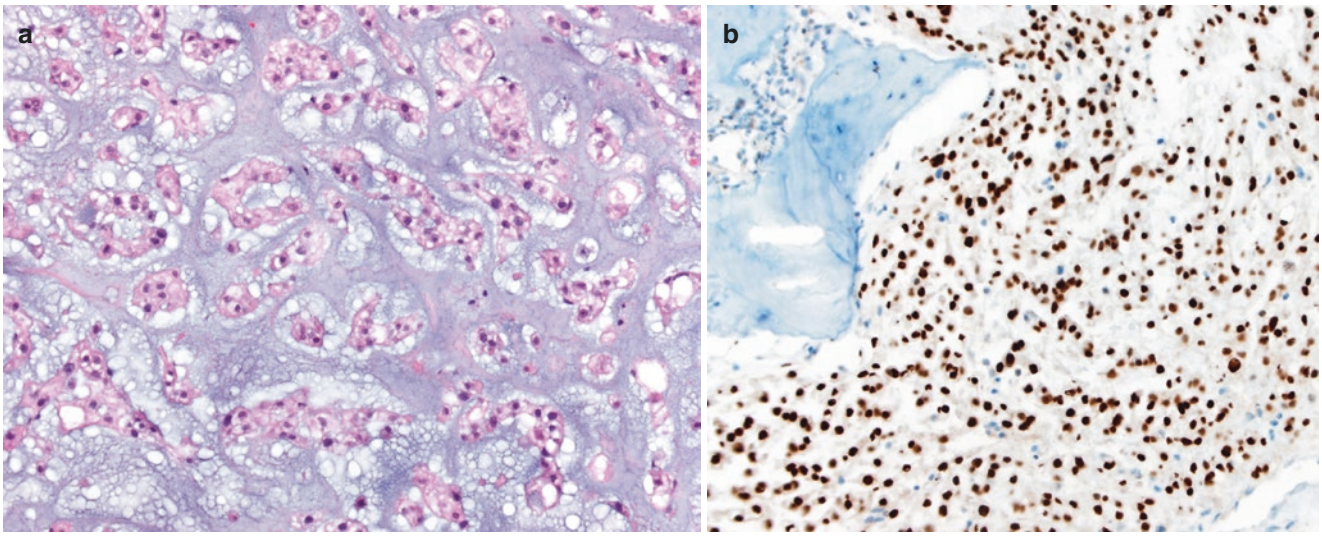

Fig. 4.3 Representative section of a chordoma showing nests and cords of cells with intracytoplasmic vacuoles (physaliphorous cells) embedded in a myxoid matrix (**a**). Chordoma cells also show diffuse nuclear positivity for brachyury immunohistochemical staining (**b**)

which undergoes enchondral ossification to form an underlying bony stalk of cancellous bone surrounded by fatty marrow. The cartilage cap typically contains chondrocytes with enlarged and hyperchromatic nuclei which can be mistaken for malignant chondrocytes if taken out of context with the organized architectural growth pattern. Since they contain an epiphysis, they can continue to grow until skeletal maturity; however, for lesions which continue to grow following maturity, malignant transformation needs to be ruled out.

These lesions are often found incidentally; however, in the pelvis, it can lead to nerve compression symptoms. Typically, the tumors are covered by a cartilage cap measuring <2 cm thick, and although malignant transformation is rare, it is more common in patients with multiple osteochondromas. Similar to tumors with continued growth, larger lesions with poorly defined cartilage cap and irregular calcifications are suggestive for malignant transformation into a chondrosarcoma [43]. Histologically, secondary chondrosarcoma arising in osteochondroma demonstrates nodular masses of neoplastic cartilage separating from the main mass and permeating through the surrounding soft tissue [44]. In general, it is extremely difficult, if not impossible, to make the diagnosis on limited biopsy tissue due to the increased amount of cytologic atypia seen in osteochondromas. Radiologic correlation usually provides compelling evidence for malignant transformation. Although these tumors can be treated expectantly, if there are signs of nerve compression or malignant transformation, they should be removed.

Giant Cell Tumor

Although classified as a benign neoplasm, giant cell tumor (GCT) is a locally aggressive tumor with the ability to metastasize to the lungs [45]. In the pelvis, these tumors most commonly involve the sacrum; however, compared to GCT in the extremities, the incidence of tumors in the pelvis is rare [46]. Histologically, these tumors are composed of neoplastic mononuclear cells without cytologic atypia admixed with numerous osteoclast-like giant cells (Fig. 4.4). The tumor cells contain round- to oval-shaped nuclei resembling those within the giant cells. Histologic heterogeneity including areas with spindled cells, necrosis, vascular invasion, cystic change, and reactive bone formation can create diagnostic challenges. Careful attention paid to the bland cytologic features of the mononuclear cells will help avoid a mistaken diagnosis of malignancy. Recently, recurrent somatic driver mutations in H3 histone family member 3A (H3F3A) (located at 1q42.12) have been identified in 92% of giant cell

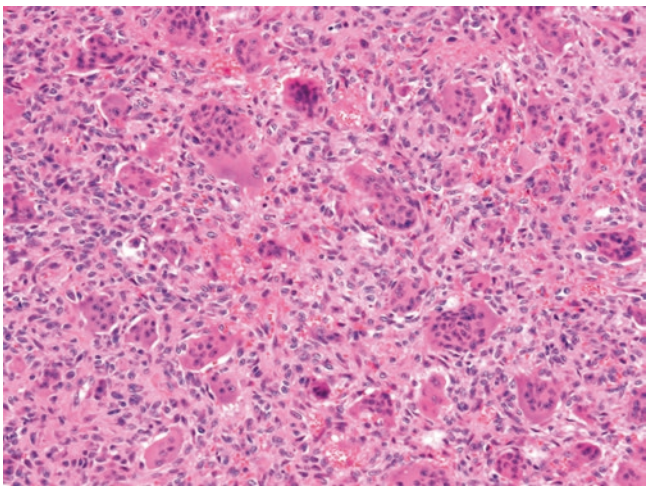

Fig. 4.4 Representative section of a giant cell tumor of bone showing neoplastic mononuclear cells without cytologic atypia admixed with numerous osteoclast-like giant cells

tumors of bone [47]. This finding leads to the development of immunohistochemistry for histone H3G34W, a highly sensitive marker for giant cell tumors which can be useful in challenging cases and core needle biopsy tissue [48, 49].

Treatment for GCT of the pelvis is controversial, ranging from intralesional curettage to a wide local excision with reconstruction [46, 50, 51]. One of the most difficult areas to treat these tumors is the periacetabular region of the pelvis, where patients undergoing an intralesional procedure have been shown to have an improved clinical outcome compared to a prosthesis [51]; however, this is outcome is worse compared to an intralesional procedure at another site in the pelvis [50]. The use of treatment adjuvants such as denosumab, which inhibits osteoclasts, has been used for the treatment of GCT in areas that are thought to be "unresectable" or for tumors which have metastasized [52]. Histologically, denosumab-treated tumors show a loss of the multinucleated osteoclast-like giant cells and replacement by variable amounts of fibrosis and woven bone. Therefore, it is important for pathologists to be aware of neoadjuvant therapy so as to avoid misdiagnosis of a benign or malignant bone-forming neoplasm.

Aneurysmal Bone Cyst

An aneurysmal bone cyst (ABC) is a benign, expansile osteolytic tumor containing blood-filled cystic spaces. In the pelvis, these tumors can be locally aggressive, with the most common location being the flat bones, particularly the sacrum and periacetabular region [53, 54]. Histologically, the tumors contain blood-filled spaces surrounded by a cyst wall composed of bland, slender spindled cells, scattered multinucleated osteoclast-type giant cells, and variable amounts of reactive woven bone which sometimes has a dark blue color. Solid areas of ABC containing the same histologic features of a cyst wall may be focal or the predominant feature. FISH for *USP6* gene rearrangement may be a helpful diagnostic tool since they are found in approximately 70% of cystic ABC [13]. The low-magnification appearance simulates telangiectatic osteosarcoma; however, ABC lacks the high degree of cytologic atypia characteristic of telangiectatic osteosarcoma. Solid areas of ABC resemble GCT. Radiologic correlation, immunohistochemistry for histone H3G34W, and/or FISH testing for *USP6* gene rearrangement can be helpful in making the distinction.

Treatment of these tumors is challenging and is individualized based on the tumor location, extent, and local bony destruction. We recommend treatment based on the size of the tumor, with tumors ≤5 cm with minimal bony destruction and do not threaten the integrity of the sacroiliac joint or acetabulum, treated with an intralesional procedure including exteriorization of the tumor, with or without an additional bone grafting procedure. For tumors >5 cm, large areas of bony destruction, or those which disrupt the sacroiliac joint or acetabulum, we recommend a more aggressive approach with resection and subsequent reconstruction of the defect [54]. Likewise, due to the propensity to bleed, we recommend for selective embolization for tumors involving the sacrum and acetabulum [54].

4.4 Summary

This chapter focuses on the pathologic features of commonly encountered pelvic tumors. The differential diagnosis of a pelvic tumor is broad, but through the use of appropriate imaging studies, combined with histologic examination of tissue with or without ancillary studies, a diagnosis can be ultimately made in a majority of patients.

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