Osteoblastoma:

Clinicopathologic Study of 306 Cases

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The clinical, radiologic, and pathologic features of 306 osteoblastomas were analyzed. Seventy-five were Mayo Clinic cases and 231 were from consultation files. Males outnumbered females two to one. The age range was 6 months to 75 years (mean age, 20.4 years). The vertebral column including the sacrum was the most frequent site (32%). Pain was the usual complaint and neurologic findings were associated with vertebral tumors. Although most tumors were well circumscribed, cortical expansion and destruction were common radiographic findings (39%), and 12% had features suggestive of malignancy. Large, epithelioid osteoblasts were seen in 24% and were the predominant cellular element in 10%. A distinctive epithelioid multifocal pattern was recognized. Recurrence rates were 16% (Mayo Clinic cases) and 21% (consultation cases). Tumors involving the central neuraxis were associated with greater morbidity and mortality. Aggressive behavior is within the biologic spectrum of osteoblastomas, and histopathology alone does not appear to be a reliable predictor of aggressiveness. The most important differential diagnosis is osteosarcoma. HUM PATHOL 25:117–134. Copyright © 1994 by W.B. Saunders Company

Osteoblastoma (OB) is an uncommon, benign bone tumor accounting for only approximately 1% of all bone tumors seen at the Mayo Clinic. Osteoblastoma was first described in the English literature in 1932 by Jaffe and Mayer[1] in a report of a case of an osteoblastic osteoid tissue-forming tumor of a metacarpal bone. Those investigators suggested that Virchow[2] may have actually published the first description in 1863. Reports of this tumor under various names, such as "osteogenic fibroma of bone"[3] and "giant osteoid osteoma" (OO),[4] subsequently appeared in the literature; the tumor was given its current name in 1956 when Jaffe[5] and Lichtenstein[6] independently proposed the term "benign osteoblastoma."

Because patients with OB can present with a broad spectrum of radiographic[7] and histologic features, the correct diagnosis may sometimes be missed. In our experience one of the most challenging problems in orthopedic pathology can be differentiation of OB from osteosarcoma (OS), especially when the specimen is small. This problem may be complicated by the fact that OBs are often progressive tumors with a propensity for locally aggressive growth; up to 25% of patients may present with radiographic features that may indicate malignancy.[7] Osteoblastomas also may have histologic features that may indicate malignancy, such as large epithelioid osteoblasts and bizarre degenerated cells that may be confused with malignant cells,[8] a multifocal growth pattern that mimics permeation, and atypical patterns of bone and osteoid. Because of such variation, several investigators[9-11] proposed the classification of a borderline osteoblastic tumor that has radiographic and histologic features intermediate between those of OB and OS. The term "aggressive osteoblastoma" is the preferred designation for this entity, a tumor defined as having locally destructive behavior, yet with no metastatic potential. Descriptions of this entity, however, are confined to a handful of series and several case reports.[9-24] In our opinion, whether aggressive OB should be considered a distinct clinicopathologic entity has not been completely resolved.

There are rare reports[7,22,25-28] of OBs that have undergone malignant transformation. One problem is inherent in such cases: because OSs can have microscopic foci indistinguishable from OBs,[10,29-31] some of these tumors that had not been adequately sampled might have actually been OSs from their onset. Malignant transformation of benign bone tumors, however, is a well-known phenomenon,[32,33] and we think that such transformation also is possible in OBs. A well-documented case was reported[7] by one of us.

At the opposite end of the spectrum differentiating a small, incipient OB from an OO also can be problematic. Because there is a close histologic relationship between these two lesions it may be impossible to tell them apart purely on the basis of histologic features.[30] For this reason Schajowicz and Lemos[34] proposed that OB and OO be considered variants within the same family of benign bone tumors. We, however, believe that an attempt should be made to distinguish between these lesions because OB has a greater tendency to progress and to recur. The cardinal feature differentiating OB from OO has been tumor size, and various limits have been arbitrarily set.[5,7,35] In this study we included no

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Key words: aggressive osteoblastoma, bone tumors, osteoblastoma, osteosarcoma.

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0046-8177/94/2502-0002$5.00/0

TABLE 1. Cases Excluded Because the Specimens Were Nondiagnostic of Osteoblastoma

Diagnosis	No. of Cases
OS	15
Aneurysmal bone cyst	6
OO	4
Inadequate specimen	4
Giant cell tumor	3
Fibrous dysplasia	3
Metaphyseal fibrous defect	2
Hemangioma	2
Hemangioendothelioma	1
Chondromyxoid fibroma	1
Pigmented villonodular synovitis	1
Total	42

lesion less than 1.0 cm in greatest dimension unless it recurred as a larger tumor with unequivocal features of OB.

To gain a better understanding of the biologic behavior of OB we undertook a retrospective study of 306 cases. We documented the demographic and clinical features, skeletal distribution, radiographic and pathologic features, types of treatment, and outcomes. We evaluated each tumor with respect to a group of histologic variables and correlated these findings with the radiographic features and clinical outcomes. We were especially interested in finding pathologic features that would be useful in differentiating OB from OB-like OS[20] and determining whether histopathology might be useful in predicting an aggressive course (aggressive OB).

MATERIALS AND METHODS

We reviewed all cases designated as OB that had histologic material available from the files of the Mayo Clinic through 1990. This included patients treated at the Mayo Clinic as well as consultation material from the files started by Dr David C. Dahlin. The histologic material from 348 cases was independently evaluated by two of us (D.R.L. and K.K.U.) without prior knowledge of the clinical or radiographic findings. Forty-two cases were eliminated because the specimens

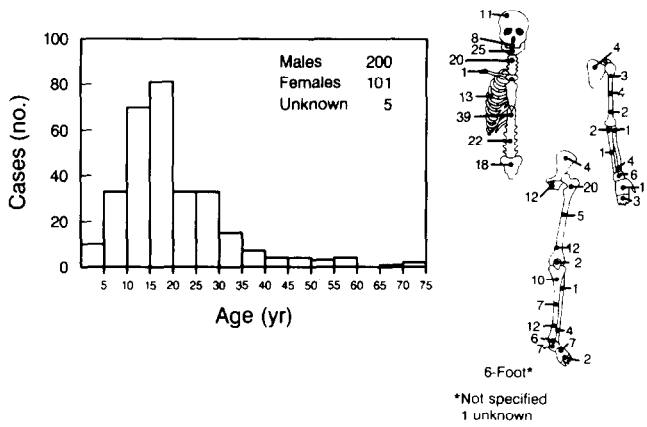

FIGURE 1. Distribution of cases by age, sex, and skeletal location for 306 OBs.

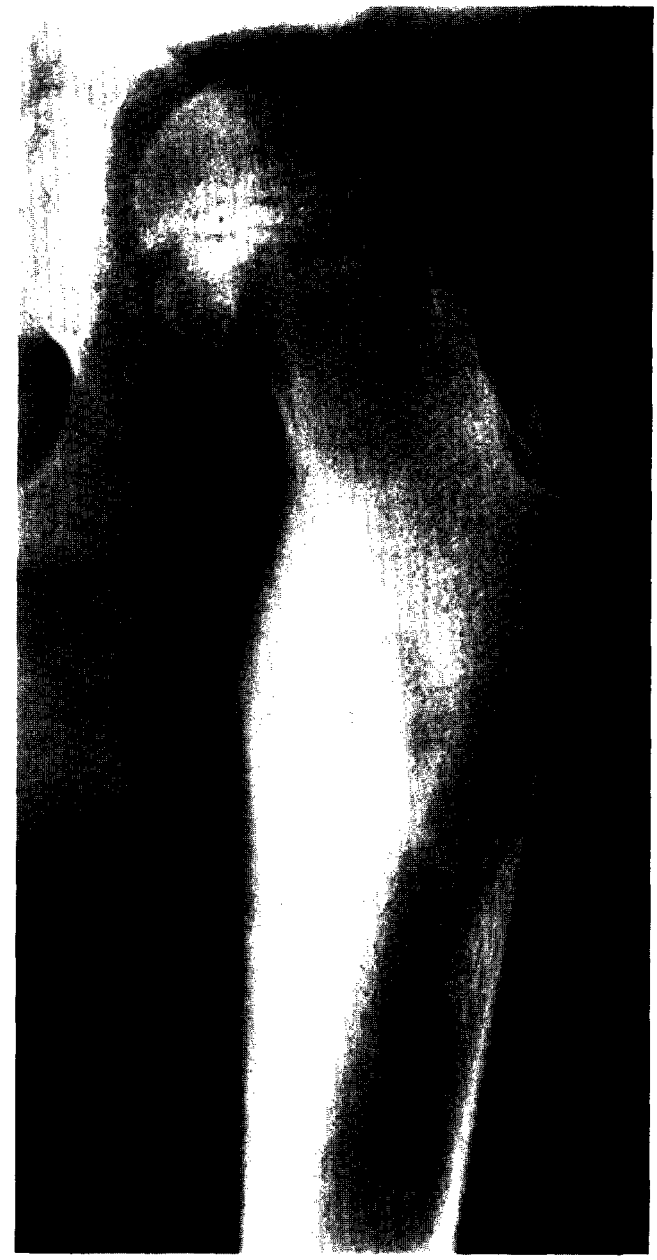

FIGURE 2. Osteoblastoma of the proximal femur resembling OO except for the large size.

were not diagnostic of OB (Table 1), including 15 cases reclassified as OS for which the reclassification was confirmed by clinical follow-up information. The final study group comprised 306 cases: 75 Mayo Clinic cases and 231 consultation cases.

Radiographic material from 198 cases was reviewed (R.A.M.): 116 radiographs from the appendicular and 82 from the vertebral skeleton. Each tumor was evaluated for size, mineralization, margination, reactive sclerosis, periosteal changes, cortical expansion and destruction, and appearance (benign, malignant, or indeterminate).

Each tumor was evaluated for the presence of the following histologic features: (1) permeation of adjacent bone or soft tissue, (2) mitotic activity, (3) large epithelioid osteoblasts (defined as cells at least twice the size of ordinary osteoblasts, with abundant eosinophilic cytoplasm and large vesicular nu-

TABLE 2. Radiographic Findings From 182 Osteoblastomas

Finding	Percentage of Cases
Appendicular skeleton (116 cases)	
Location	
Cortex	65
Medulla	35
Surface	5
Size: 0.9-11.0 cm (mean, 3.18 cm)	
Appearance	
Benign	72
Malignant	10
Indeterminate	17
Cortical destruction	25
Vertebral skeleton (66 cases)	
Location	
Dorsal elements	55
Dorsal elements plus vertebral body	42
Size: 1.0-15.0 cm (mean, 3.55 cm)	
Appearance	
Benign	52
Malignant	15
Indeterminate	33
Cortical destruction	62

clei containing prominent nucleoli)[10]—we also noted whether they were the predominant cellular element (ie, at least 75% of the osteoblasts), (4) areas of secondary aneurysmal bone cyst (ABC), (5) bizarre degenerated cells, (6) clusters of osteoblasts with no intervening osteoid matrix, (7) areas of necrosis or infarct, (8) fine lacelike osteoid, (9) chondroid differentiation (either chondroid matrix or true hyaline cartilage), (10) spiculated blue bone (defined as immature, irregular, densely calcified osteoid, as is sometimes found in OS),[9,11] and (11) multifocality (defined as the presence of multiple growth centers or nidi, separated by variable amounts of reactive bone or spindle cell stroma, within a single area of tumefaction).

Clinical information was obtained from the medical records (Mayo Clinic cases) and from correspondence with the referring physicians (consultation cases). The Mayo Clinic cases were evaluated separately from the consultation cases because the clinical histories of the former, which included detailed surgical information, were available in every instance.

RESULTS

General Information

The study group had 200 male and 101 female patients (Fig 1). We had no information about the sex of five patients. Ages ranged from 6 months to 75 years (mean age, 20.4 years); 75% of patients were 25 years old or younger. The ages of five were not known.

Locations

Virtually every bone in the body was affected (Fig 1). The vertebral column was the most frequent site, which, including the sacrum, accounted for 32% of the

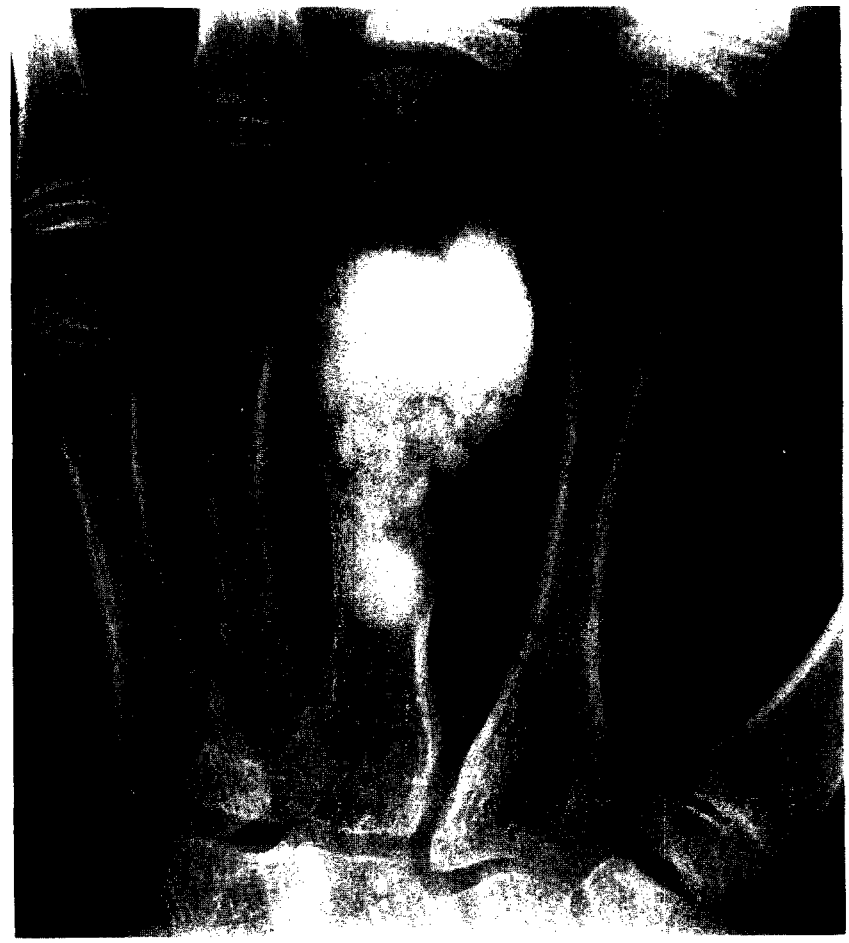

FIGURE 3. Osteoblastoma of the third metacarpal shows ossification and cortical expansion.

FIGURE 4. Osteoblastoma of the acetabulum. The radiographic appearance suggests malignancy.

tumors. The femur was the second most common site (12%), followed by the jaw bones (11%), tibia (10%), and foot and ankle region (9%). One tumor was situated in the soft tissue of the hand.

Signs and Symptoms

Pain, often progressive, was the most frequent complaint, identified in 87% of the Mayo Clinic patients. Local swelling, tenderness, warmth, and gait disturbances also were mentioned frequently. The average duration of these complaints was 2 years. Ten Mayo Clinic patients presented with neurologic complaints (secondary to spinal tumors) that ranged from numbness and tingling to paraparesis and paraplegia. Painful scoliosis was the initial finding in four cases. Other less common signs and symptoms included fever, weight loss, night pain, headaches, epistaxis, tooth impaction, and significant aspirin usage.

Radiographic Findings

Appendicular Osteoblastoma. Radiographs were available for review in 116 cases of appendicular OB (Table 2; Figs 2, 3, 4, and 5). Sixty-five percent of the tumors were located within the cortex and the remaining 35% were in medullary locations. Six tumors arose on the bone surface. Of the tumors that occurred in the long bones, 42% were metaphyseal and 36% were diaphyseal. The remaining 22% were located within the epiphysis.

Tumor size was quite variable, ranging from 1.0 to 11.0 cm. The average size was 3.18 cm. Approximately one quarter of the tumors were less than 2 cm in size. The margin was well defined and distinct in two thirds of the tumors. The margin was intermediate in 21% and ill defined in 13%.

The interior of the tumor showed various degrees of ossification in half of the cases. Serial films from several patients indicated that younger lesions are sometimes lucent but tend to ossify with maturity. In eight tumors central calcification was identified. This appearance is highly suggestive of OB. Reactive sclerosis of adjacent normal bone was seen in 58%. Periosteal new bone formation also was fairly common (36%). In most cases the new bone was the benign solid type, but examples of spiculation, multilamination, and Codman's

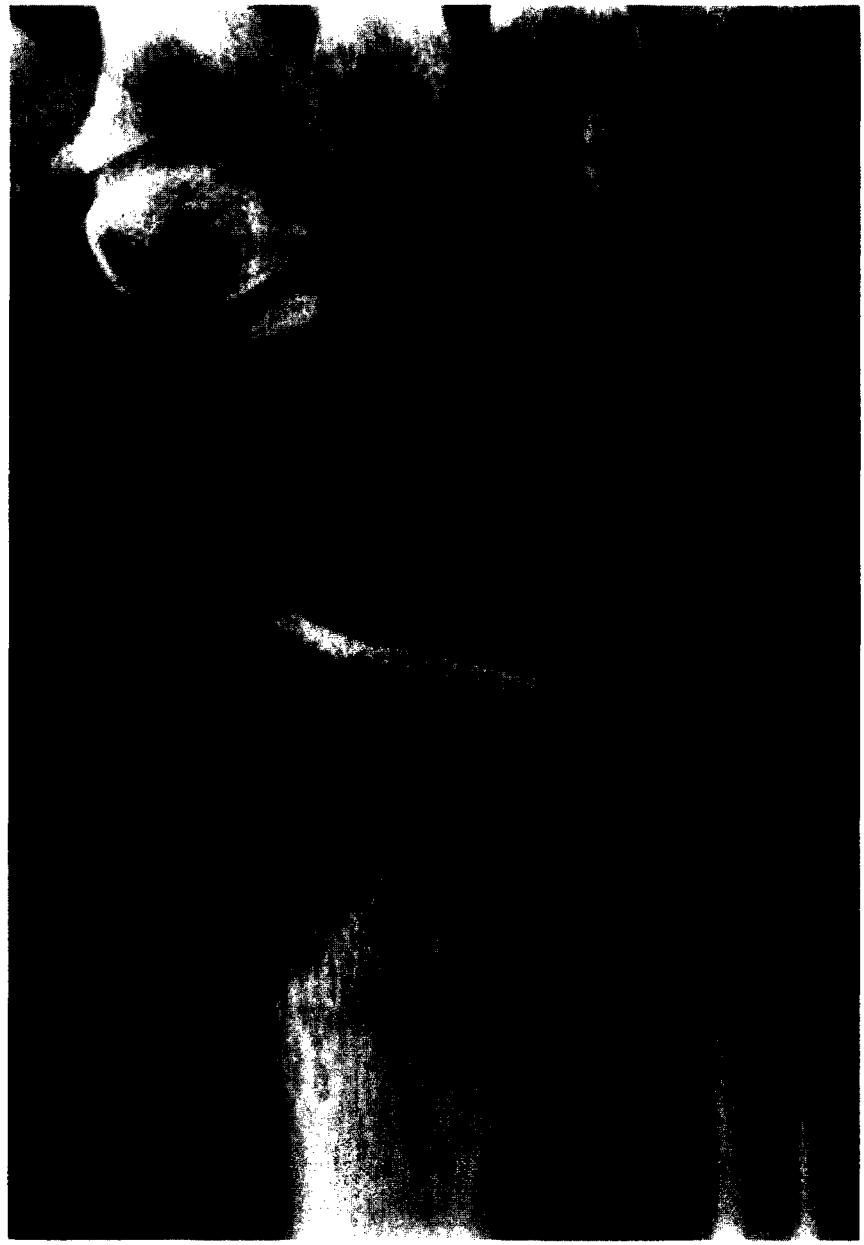

FIGURE 5. Osteoblastoma of the distal radius has a nonspecific radiographic appearance. Note the poor margination.

triangles suggestive of a more aggressive lesion were all seen. An ossified tumor surrounded by a lucent halo was seen in nine cases and suggested this diagnosis. Thirty of these tumors had a radiographic appearance similar to OO, except for their large size.

Expansion of the adjacent cortical bone was present in 72% of cases. Definite cortical destruction or penetration suggestive of a more aggressive lesion occurred in 25% of these OBs. Pathologic fracture was present in five patients.

Based solely on the radiographs of these tumors, 72% were thought to have a benign appearance and 10% were thought to be malignant. The remaining 17% were considered to be indeterminate.

The radiographic appearance was thought to indicate OB in 43% of these cases. In one quarter of the cases the radiographic appearance was not considered specific for any particular diagnosis. In 17% of the cases a diagnosis of OO was suggested. Because of the varied radiographic appearance of this tumor many other diagnoses were suggested. In descending order of frequency, these were chondroblastoma, OS, ABC, fibrous dysplasia, chondrosarcoma, osteomyelitis, giant cell tumor, and Ewing's sarcoma.

Vertebral Osteoblastoma. Of the 66 OBs in the vertebral column, 21 were cervical, 14 thoracic, 18 lumbar, and 13 sacral (Figs 6, 7, and 8). Involvement of the vertebral body alone was rare. Fifty-five percent of the lesions were contained entirely within the dorsal elements, whereas 42% affected both the dorsal elements and the adjacent vertebral body.

The largest dimension of these tumors varied from 1.0 to 15.0 cm. The average size was 3.55 cm. Tumor margination was considered good, intermediate, or poor; each of these three types was seen with equal frequency.

FIGURE 6. Osteoblastoma of the cervical spinous process. Note the expansion and ossification.

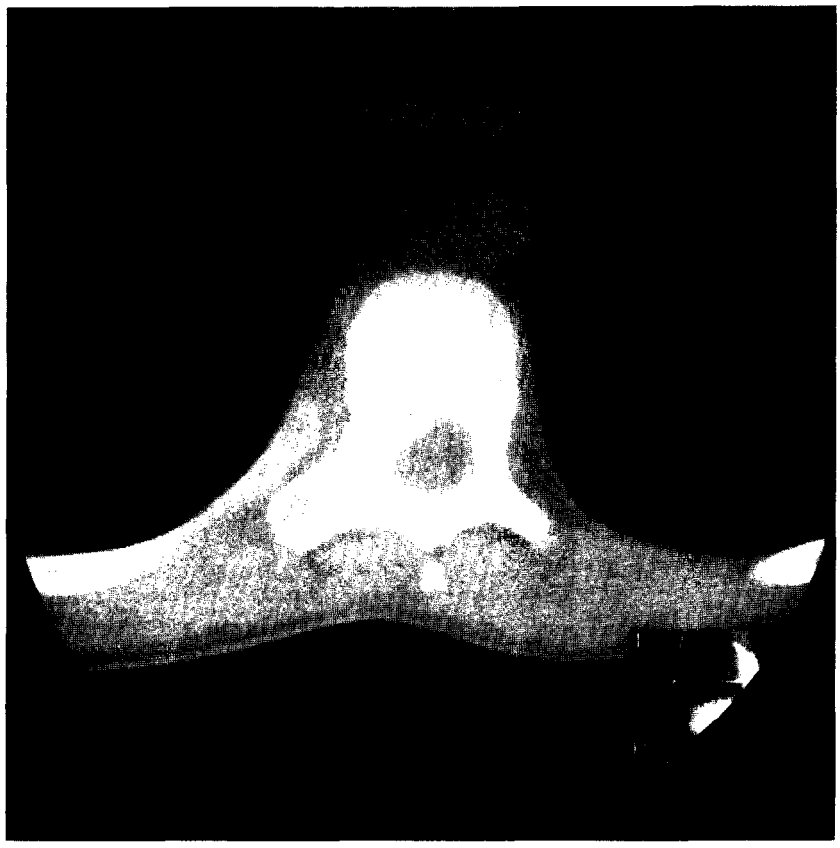

FIGURE 7. Typical OB of the thoracic spine pedicle. Note the ossification and lucent halo.

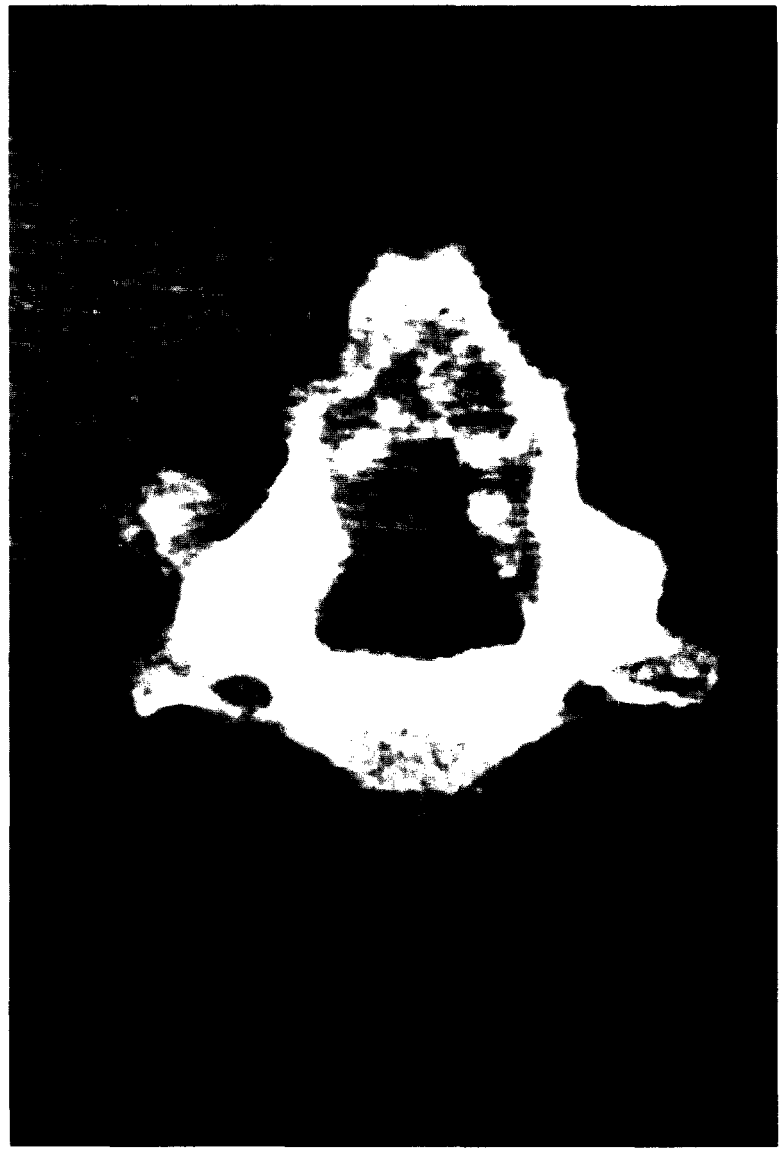

FIGURE 8. Osteoblastoma of the cervical spine showing cortical destruction that may indicate malignancy.

The interior of the tumor was mineralized in 55% of cases. Central calcification was seen in five patients. Sclerosis of the adjacent bone occurred in 59% of these tumors. In a few cases sclerosis was the only radiographic finding. A lucent halo surrounding a mineralized tumor was seen in three instances.

Cortical expansion was seen in 64% of the tumors and areas of cortical destruction were present in 62%. The presence of both expansion and destruction was common. Pathologic fracture was present in three patients. A missing pedicle was the sole finding in two cases, and in two additional patients radiographic findings were normal.

Retrospectively, based on their radiographic appearance we believe that 52% of these tumors were benign, 33% were indeterminate, and 15% suggested malignancy. Osteoblastoma was considered one of the two top diagnostic possibilities in 64% of these patients. One quarter of the tumors were considered to be nonspecific. The most frequent lesions in the differential diagnosis were ABC, chondrosarcoma, OS, OO, and metastasis.

Pathologic Findings

Gross Pathology. In most instances OBs are treated by curettage and the tissue is received piecemeal as red to tan, gritty friable fragments. We were, however, able to examine 10 intact resection specimens retrieved from the tissue archives. All 10 tumors had the typical color and consistency; however, the size as well as the character of the adjacent bony reaction varied. The extent of reactive sclerosis of surrounding host bone ranged from minimal to marked (Fig 9). The tumor-bone interface was sharp, sometimes with a scalloped margin. Several tumors were quite destructive. The largest tumor we saw was an 11.0-cm mass situated on the periosteal surface of the distal femur. Another large tumor emanated from a posterior rib where it formed a 6.0-cm destructive mass that involved portions of an adjacent rib and vertebral body. The bulk of it expanded

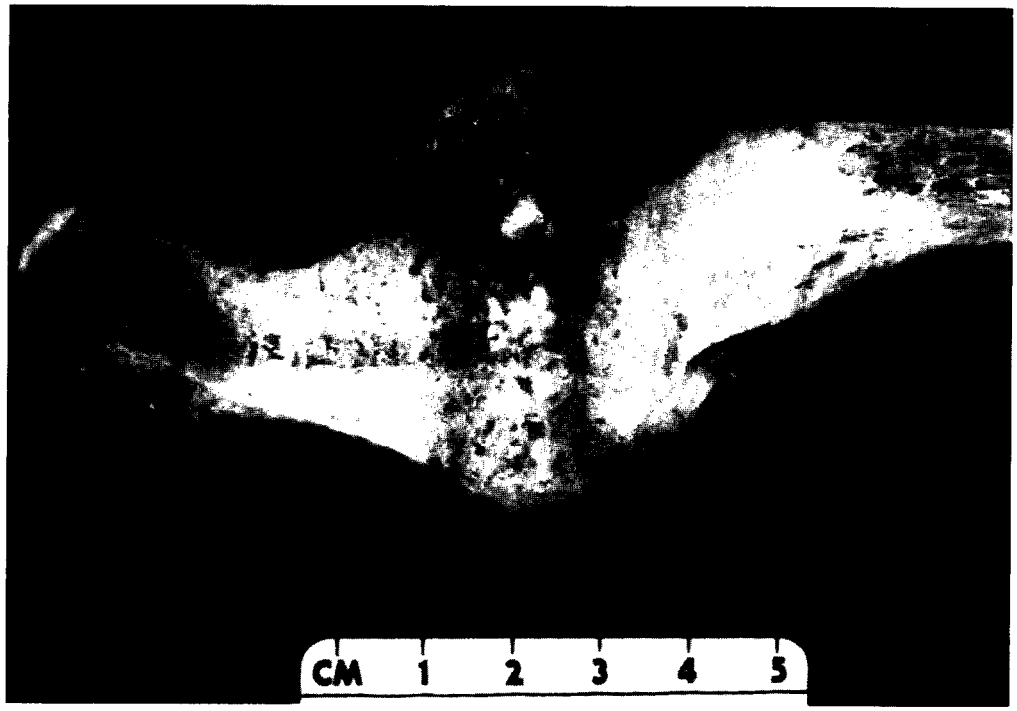

FIGURE 9. Osteoblastoma of the clavicle demonstrates a sharp scalloped margin and extensive reactive sclerosis.

into the soft tissue as a well-circumscribed mass surrounded by a bony shell.

Microscopic Pathology. Although most of the OBs we examined had classic histologic features (ie, long interanastomosing trabeculae of osteoid or woven bone rimmed by a single row of osteoblasts within a loose fibrovascular stroma) (Fig 10, top), the most striking finding was the variation in histologic patterns (Table 3). The host-tumor interface was sharp, often with the tumor showing peripheral bony maturation. Seams of tumor matrix often connected with adjacent host bone trabeculae (Fig 10, bottom). Several tumors expanded into soft tissue with a well-delimited, pushing border surrounded by a thin shell of reactive bone. Although six of the tumors appeared to interdigitate with the adjacent tissue, none showed destructive permeation, which is seen in OS.

The amount of osteoid and bone varied, not only among tumors but sometimes within a single tumor. Some OBs were composed almost entirely of solid sheets of densely calcified matrix, which entrapped the osteogenic cells. In such cases the matrix often appeared to radiate from a central focus. In other OBs the matrix was sparse and formed wispy strands of osteoid between individual cells, often preserving a trabecular architecture. Although foci of fine, lacelike osteoid were identified in 20% of cases (Fig 11), the osteoid foci never accounted for a significant portion of any tumor. The amount of bone formation was variable and usually consisted of immature woven bone. In many instances it resembled pagetoid bone with irregular, basophilic reversal lines (Fig 12).

Zones of spiculated blue bone, as described by Schajowicz and Lemos[9] (ie, irregular, densely calcified immature osteoid), were seen in 16% of our cases (Fig 13). Rarely, small "psammomatous" calcifications were seen. Focal areas containing chondroid matrix were present in 18 cases (6%), as we have reported.[36] Four of these examples contained true hyaline cartilage as part of the tumor matrix (Fig 14).

The osteoblasts usually were arranged as single units along the osteoid trabeculae. In 6% of our cases, however, osteoblasts aggregated focally in small clusters with no intervening matrix. They were never arranged in large, continuous sheets. The cells usually were polygonal and contained moderate amounts of cytoplasm. The nuclei were round to oval, with regular contours, and frequently contained single prominent nucleoli. Mitotic figures were nil to minimal in 89% of cases, moderate in 10%, and prominent in only 1%. Osteoclasts were a common complement to most tumors.

Large epithelioid osteoblasts (defined above) were identified in 24% of the tumors. They were the predominant cellular element in only 10% (Fig 15). Two thirds

TABLE 3. Histopathologic Findings From 306 Cases of Osteoblastoma

Finding	Percentage of Cases
Mitotic activity	
Nil to minimal	89
Moderate	10
Prominent	1
Epithelioid osteoblasts	
Present	24
Predominant (>75%)	10
Bizarre cells	11
Aneurysmal bone cystlike areas	10
Spiculated blue bone	16
Chondroid matrix	6
Multifocal growth pattern	14
Fine lacelike osteoid foci	20
Necrosis	2

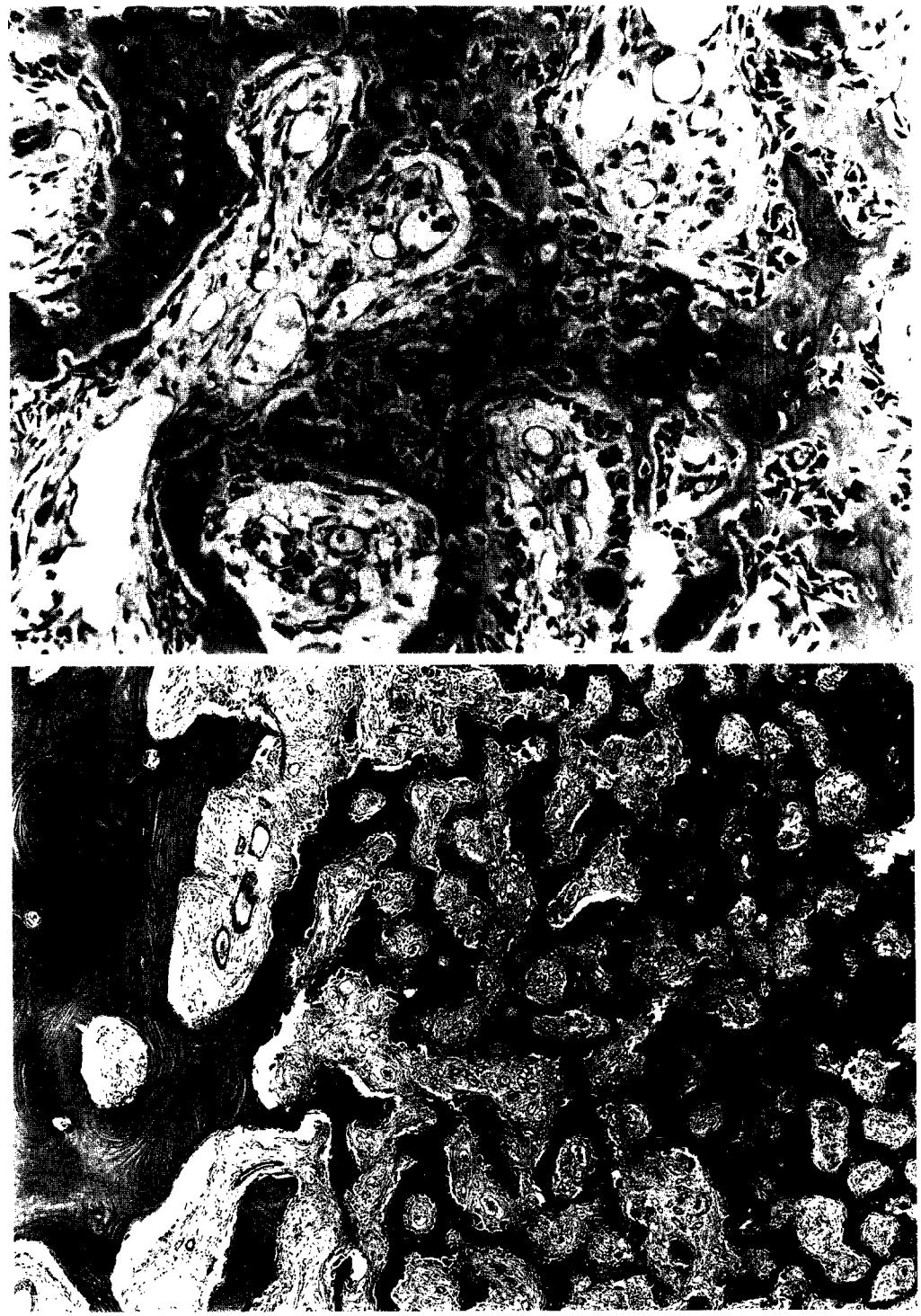

FIGURE 10. (Top) Classic histologic features of OB with long interanastomosing trabeculae of woven bone and osteoid rimmed by a single row of osteoblasts within a loose fibrovascular stroma. (Hematoxylin-eosin stain; original magnification ×250.) (Bottom) Peripheral edge of OB with sharp bone-tumor interface and seams of tumor matrix connecting with adjacent host bone. (Hematoxylin-eosin stain; original magnification ×50.)

of these epithelioid osteoblast-predominant tumors also had a multifocal pattern. Bizarre cells (ie, cells with large degenerate nuclei with smudged chromatin) were seen in 11% of the tumors. These cells rarely accounted for a significant proportion of any tumor; when they did they gave the tumor a pseudosarcomatous appearance (Fig 16).

The stroma was composed of loosely arranged fibrovascular tissue with many capillaries. In some instances the stroma was more cellular and spindly, and in 10% of cases there were areas of secondary ABC.

Forty-three of the OBs (14%) were multifocal (more than one nidus within a single tumor). The nidi were separated by either trabeculae of woven bone or a spindled stroma (Fig 17, top). More than half of these tumors contained a predominant component of epithelioid osteoblasts (Fig 17, bottom). Foci of infarctlike coagulation necrosis were seen in only 2%.

Treatment and Outcome

Complete treatment and follow-up data were available for all but one of the 75 Mayo Clinic patients. The

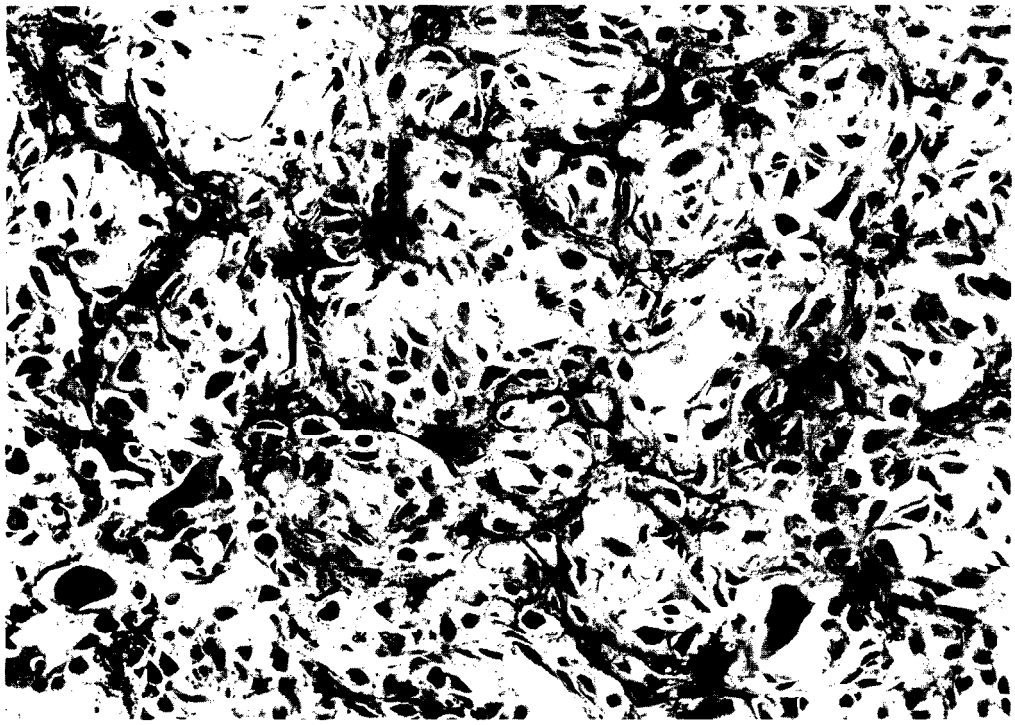

FIGURE 11. Focal areas of fine, lacelike osteoid were seen in 20% of the tumors. (Hematoxylin-eosin stain; original magnification ×400.)

mean follow-up period was 17.5 years (range, 3 months to 60 years). All 75 patients had been treated surgically. The initial treatment in 52 patients consisted of intralesional excision, including curettements with bone grafts and laminectomies for vertebral lesions. Ten of these patients (19%) had recurrences. Eighteen patients had marginal en bloc resections, and one of the 18 had a recurrence. Three patients had wide local excisions with negative margins (one recurrence) and two had amputations for tumors misdiagnosed as OSs (no recurrences). A 12-cm sacral tumor in one case underwent regression after biopsy alone; the patient is alive and well 31 years later (Fig 18).

In the Mayo Clinic group 12 tumors (16%) recurred (average time, 19.5 months). Nine of these patients were treated with intralesional re-excisions. One

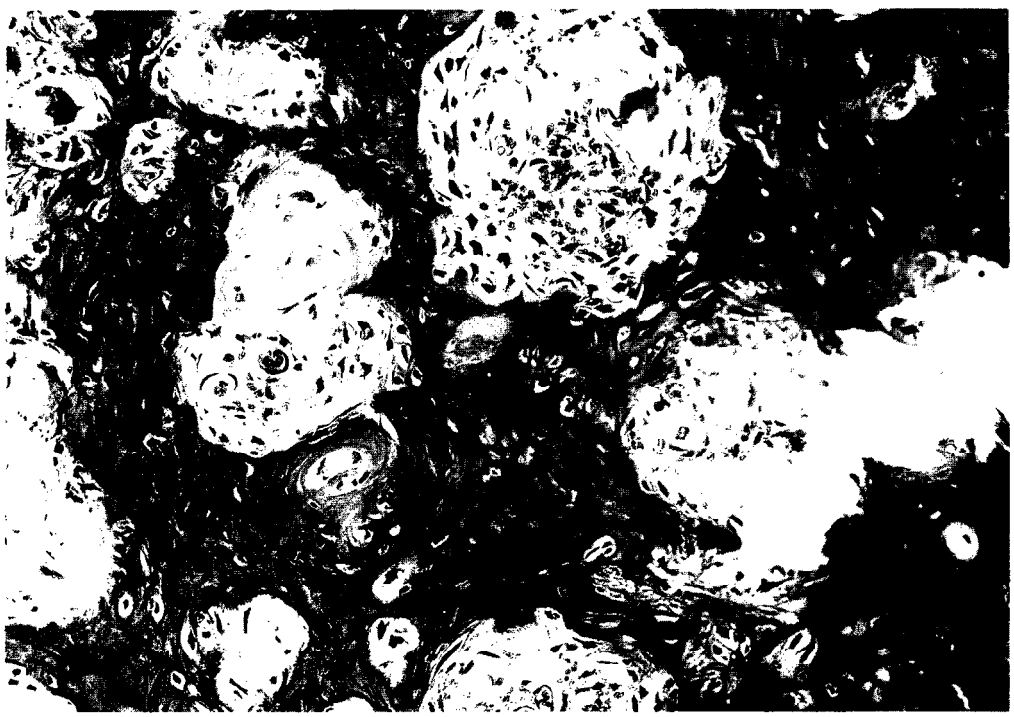

FIGURE 12. Bone with pagetoid features (ie, irregular, basophilic reversal lines) was present in many of the tumors. (Hematoxylin-eosin stain; original magnification ×250.)

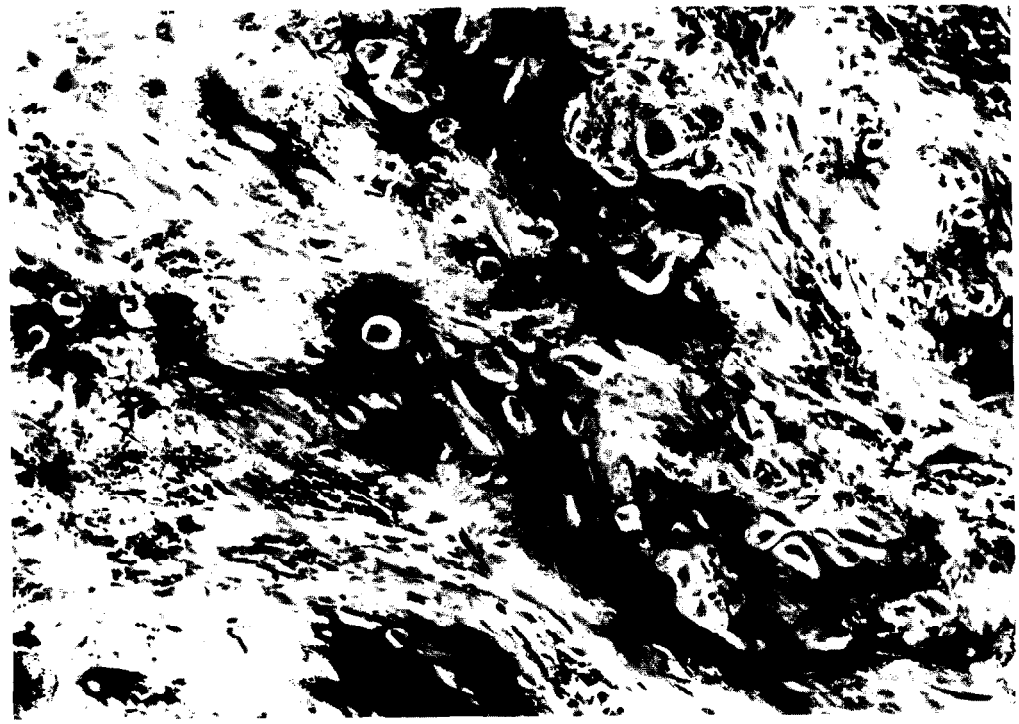

FIGURE 13. Zones of spiculated blue bone were observed in 16% of the OBs. (Hematoxylin-eosin stain; original magnification ×250.)

patient was treated with marginal en bloc resections and two with wide re-excisions. Four patients were treated for second recurrences: three with intralesional re-excisions and one with an en bloc resection. Seven patients had persistent pain after incomplete excisions. One patient had an above-knee amputation for an OB that had transformed to OS after the second recurrence (case no. 1, Table 4). One patient had preoperative chemotherapy after a mistaken diagnosis of OS. Six patients had postoperative radiation therapy, including two after subtotal tumor removal. No Mayo Clinic patient died as a result of the tumor.

Follow-up information was available in 132 of the 231 consultation cases (57%). Twenty-eight patients (21%) had recurrences, eight (6%) had second recurrences, and three (2%) had third recurrences. Four patients died: two from direct impingement of tumors on the central neuraxis, one of postoperative

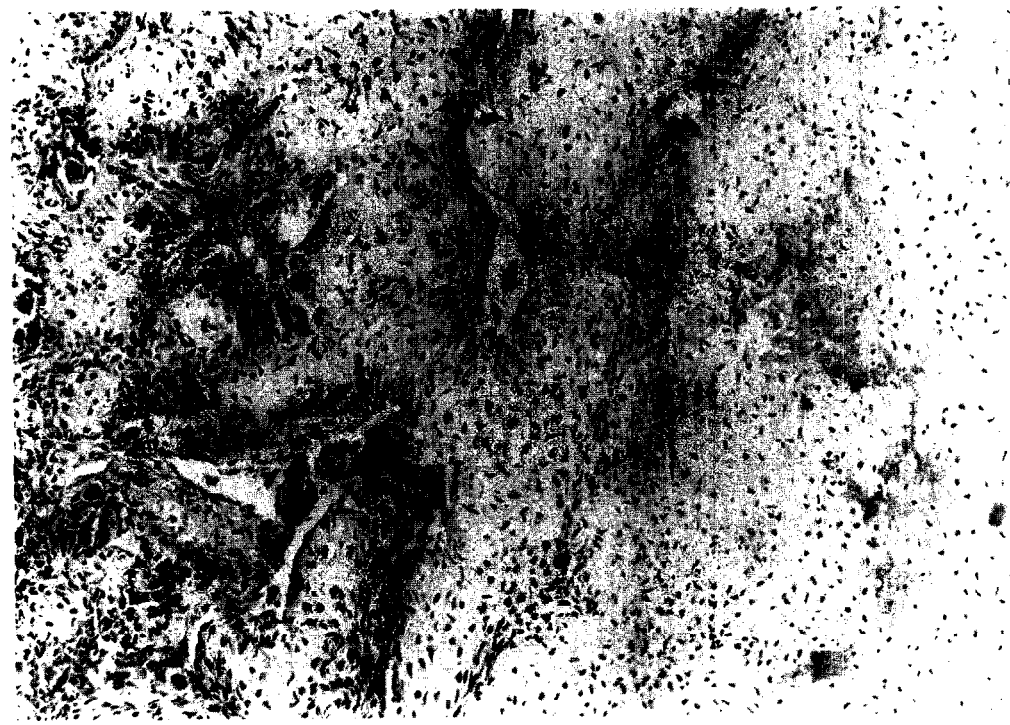

FIGURE 14. A zone of hyaline cartilage within the tumor matrix is seen merging with an otherwise typical OB. (Hematoxylin-eosin stain; original magnification ×125.)

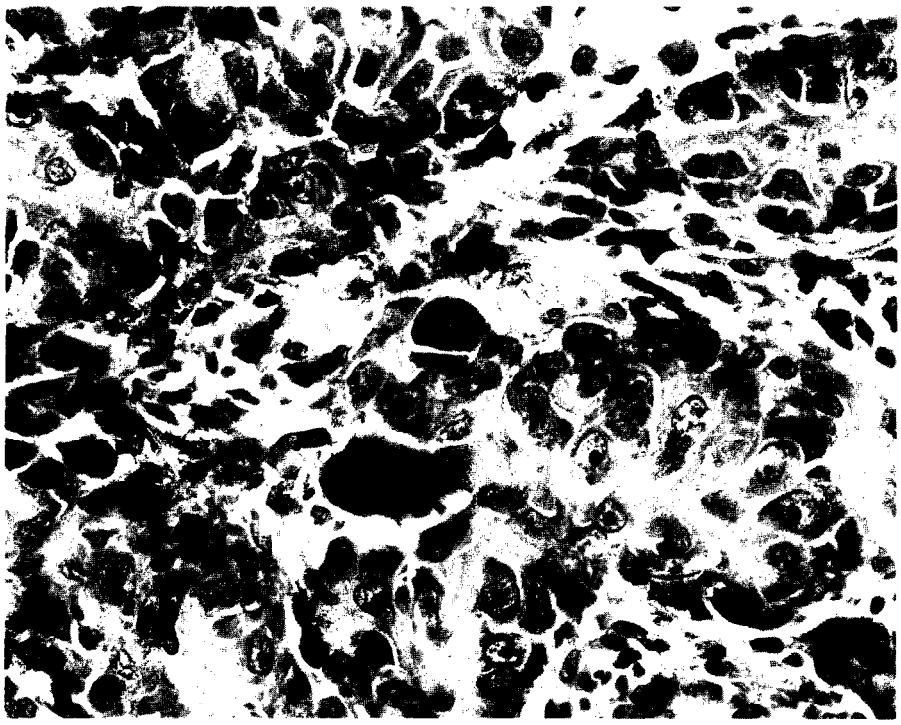

FIGURE 15. Large epithelioid osteoblasts containing abundant, usually eosinophilic, cytoplasm and large vesicular nuclei with prominent, usually solitary, nucleoli formed the predominant cellular element in 9.7% of the OBs. (Hematoxylin-eosin stain; magnification ×500.)

complications, and one of metastatic disease from an OB that underwent malignant transformation (case no. 2, Table 4). Three tumors regressed after subtotal removal.

Analysis of the Mayo Clinic cases and the consultation cases disclosed no significant differences in recurrence rates on the basis of tumor location or size. Three patients died of locally aggressive tumors, all involving the central neuraxis. One was a 27-year-old man who died of spinal cord compromise due to an upper cervical vertebral tumor with extensive secondary ABC. Another was a 6-year-old girl who died of a rapidly growing maxillary tumor that impinged on the brain. This tumor had secondary ABC as well as an epithelioid-multifocal pattern. The third patient, a 31-year-old man, died of postoperative adult respiratory distress syndrome after excision of the third recurrence of a thoracic vertebral tumor.

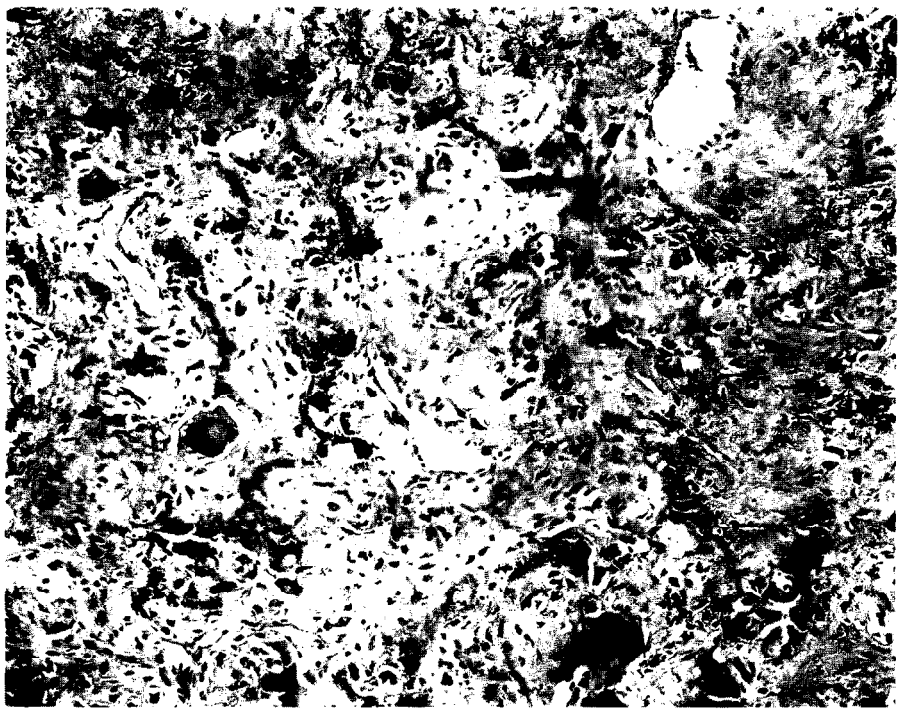

FIGURE 16. Pseudosarcomatous OB with bizarre cells containing large degenerate nuclei with smudged chromatin. (Hematoxylin-eosin stain; magnification ×200.)

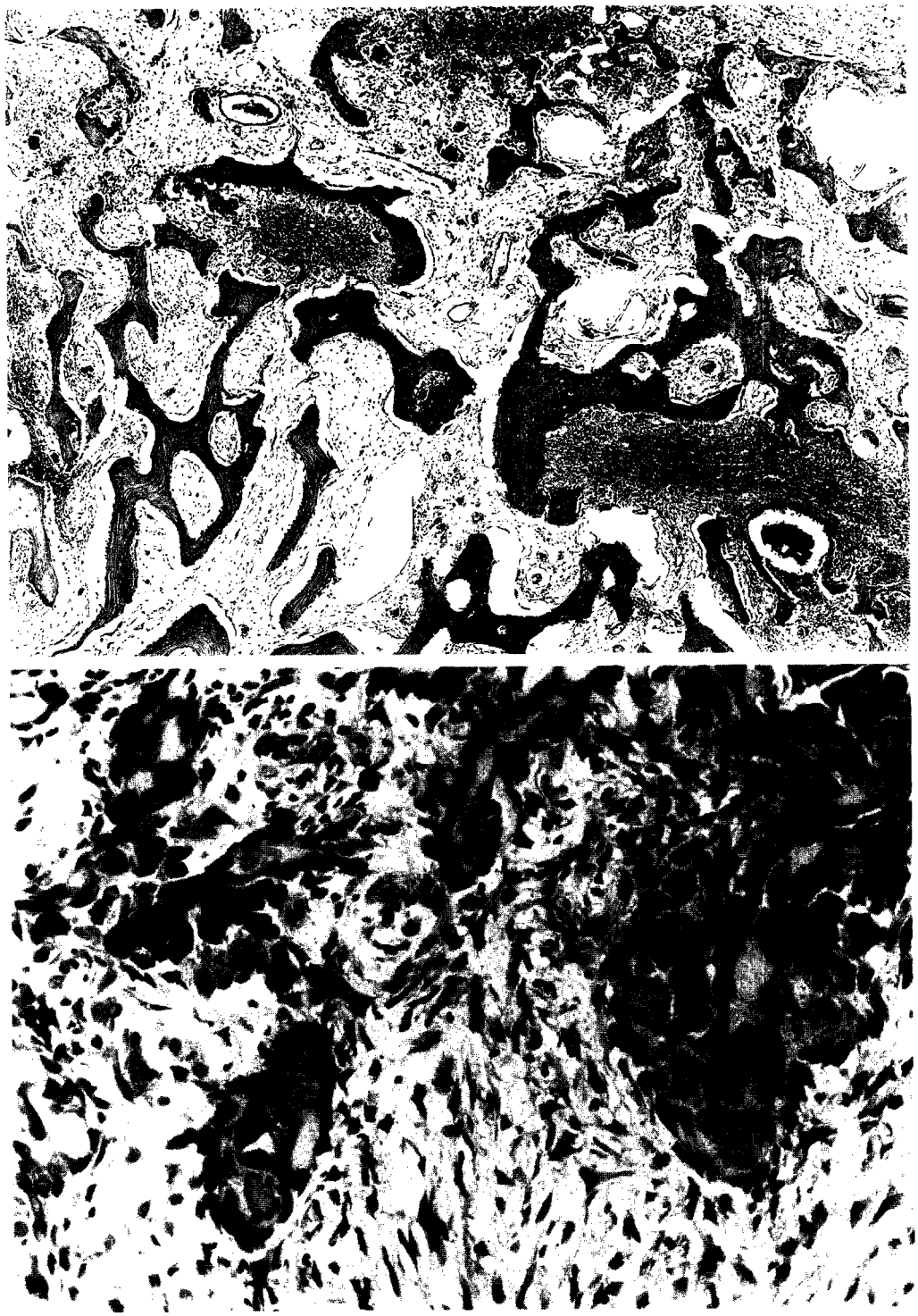

FIGURE 17. (Top) Multifocal OB with numerous nidi, or growth centers, separated by reactive bone, within a single tumor. (Hematoxylin-eosin stain; magnification ×50.) (Bottom) Many multifocal OBs were populated almost entirely by epithelioid osteoblasts. (Hematoxylin-eosin stain; original magnification ×400.)

Thirty cases (10%) were associated with histologic features of secondary ABC. Two of these tumors caused the death of the patients. Both were rapidly growing tumors that involved the central neuraxis, as described above. In another patient paraplegia developed from a vertebral tumor with secondary ABC change. The remaining patients (19 with follow-up) with tumors containing secondary ABC had no significant morbidity. The presence of chondroid matrix, spiculated blue bone, fine lacelike osteoid, bizarre cells, or prominent mitotic activity had no significant effect on outcome.

The Problem of "Aggressive Osteoblastoma"

Thirty tumors (seven Mayo Clinic cases and 23 consultation cases) were composed predominantly (ie,

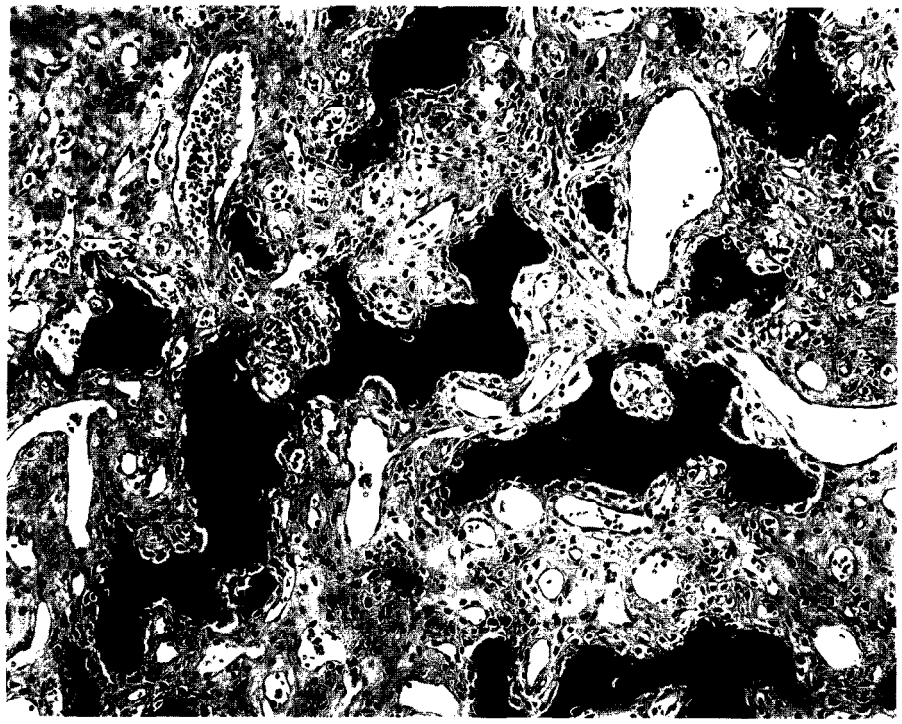

FIGURE 18. A 12-cm OB underwent complete regression after biopsy alone. (Hematoxylin-eosin stain; magnification ×62.)

>75%) of large epithelioid osteoblasts and were analyzed as a separate group to test whether this histologic feature predicted a more aggressive clinical course, as has been suggested by other investigators[9-11,15] (Table 5). These tumors tended to be more mitotically active (40% had prominent mitotic activity) than conventional OBs. Two thirds had a multifocal growth pattern. They ranged from small, clearly benign to large, aggressive tumors (range, 1.3 to 11.0 cm; mean, 4.1 cm). Eleven of the 20 tumors (55%) for which radiographic material was available were considered to be benign, five (25%) had features that suggested malignancy, and four (20%) were considered to be indeterminate.

TABLE 4. Osteoblastoma With Malignant Transformation

Case No.	Age (yr)	Sex	Site	Outcome
1	16	M	Tibia (mid-shaft)	First recurrence as OB (22 mo); second recurrence as OS (40 mo); above-knee amputation (40 mo); excision of pulmonary metastases three times; currently alive and well (23 yr after treatment)
2	14	F	Thoracic vertebra (dorsal elements)	First recurrence as OB (20 mo); second recurrence as OB (48 mo); third recurrence as OS (60 mo); pulmonary metastases and death (8 yr 8 mo after initial treatment)

Four of the seven Mayo Clinic patients with epithelioid tumors had aggressive surgical management. Two had marginal en bloc excisions: one for a cervical vertebral tumor and one for a 6.0-cm rib tumor. One patient had a wide excision of a tumor in the clavicle (Fig 9) and one had an above-knee amputation for an 11.0-cm periosteal tumor in the femur. These last two cases had been misdiagnosed as OS preoperatively. The other three patients had intralesional excisions. There were no recurrences.

Follow-up information was available in 14 of the 23 consultation cases with epithelioid tumors. Three patients had recurrences and one had two additional recurrences. Two of these patients died: one of disease due to an aggressive tumor in the maxilla (case no. 28, Table 5) and the other from postoperative complications after excision of a recurrent vertebral tumor (case no. 30, Table 5).

Osteoblastoma With Malignant Transformation

Two cases of OB, benign histologically at initial presentation, underwent malignant transformation to high-grade osteoblastic OS (Table 4). Both recurred multiple times in several years before becoming malignant. The first patient, a 16-year-old boy, presented with a 5-cm tibial tumor. The tumor recurred twice during the ensuing 3 years before a diagnosis of malignancy was made. He ultimately underwent amputation, followed by multiple resections of pulmonary metastases. He currently is alive and well after 23 years. The second patient, a 14-year-old girl, presented with a thoracic ver-

TABLE 5. Clinicopathologic Findings From 30 Cases of Epithelioid-Predominant Osteoblastoma

No.* Case	Age (yr)	Sex	Site	Size (cm)	Radiographic Appearance	Mitotic Activity	ABC	Multifocal Growth Pattern	Treatment	Outcome (mo)
1	18	M	Clavicle	1.3	B	++		+	WE	NED, 37
2	17	F	Femur	11.0	M			+	Amp	NED, 348
3	20	F	Mandible					+	IE	NED, 444
4	17	F	CV	2.2	B			+	ME	NED, 102
5	15	F	CV	4.0	I			+	IE	NED, 132
6	28	F	Rib	6.0	M	++			ME	NED, 63
7	31	M	TV	3.0	B	+		+	IE	NED, 58
8	9	F	Tibia	2.5	B		+	+		NED, 120
9	26	M	Femur				+	+		
10	14	M	Humerus		M		+			NED, 33
11	21	F	Pubis			+				R×1; NED, 144
12	13	M	Calcaneus	5.2	B			+		
13			Maxilla	4.8	I			+		NED, 6
14	8	F	Metatarsal	7.4	I	+				
15	53	M	TV	2.0	B			+		NED, 54
16	20	M	Rib	2.0	B	+				
17	14	M	Fibula	1.3	B	+				
18	28	M	TV	6.0	I			+		R×1; NED, 89
19	53	M	Acetabulum	5.8	M					NED, 66
20	24	F	TV					+		NED, 57
21	6	M	Femur	1.3	B	+				
22	29	M	Mandible			+		+		
23	22	M	Foot					+		NED, 39
24	16	F	Sacrum			+		+		NED, 30
25	14	F	Maxilla	3.4	B					NED, 33
26	18	M	CV					+		
27	33	M	Sacrum			+				
28	6	F	Maxilla				+	+		DOD, 20
29	21	M	Maxilla	3.5	B			+		NED, 60
30	31	M	TV	4.2	M	+		+		R×3†

Abbreviations: Amp, amputation; B, benign; CV, cervical vertebra; DOD, dead of disease; I, indeterminate; IE, intralesional excision; M, malignant; ME, marginal en bloc excision; NED, no evidence of disease; R×1, recurred once; R×3, recurred three times; TV, thoracic vertebra; WE, wide excision.

* Cases no. 1 through 7, Mayo Clinic patients; cases no. 8 through 30, consultation cases.

† Died of postoperative adult respiratory distress syndrome.

tebral tumor situated in the dorsal elements. A malignant diagnosis was rendered after the third recurrence 5 years after initial presentation. She ultimately died of metastatic disease 8 years 8 months after diagnosis.

DISCUSSION

This series of 306 cases represents the largest study of OB to date. Our results confirm the findings of previous investigators that OB is a benign tumor affecting younger patients and is more prevalent in males.[4-7,34,37-41] We found that OB has the potential for progressive growth and may sometimes pursue an aggressive clinical course. In addition, OB appears to have the potential for regression after subtotal removal. Most importantly, we found that differentiating OB from OS sometimes can be difficult. Thus, the emphasis of our study was to determine whether there are any factors that might be useful in differentiating OB from OB-like OS and in predicting aggressive behavior.

We excluded 15 cases of OS that initially had been misdiagnosed as OB. We also encountered several OBs mistakenly diagnosed as OS. These findings reflect the great difficulty sometimes encountered in differentiating these tumors, especially when dealing with a small biopsy specimen.

From a review of the 15 misdiagnosed OSs we observed several important morphologic features more likely to be found in OS than in OB. Although several of these OSs resembled OB by having a trabecular osteoid pattern, the cells between the trabeculae tended to be arranged in a compact pattern (Fig 19, top), unlike the looser, more polymorphic pattern seen in OB.[31] These cells were more likely to form clusters or sheets without intervening matrix and to show greater nuclear hyperchromasia and mitotic activity. The presence of cartilaginous matrix, once believed to exclude a diagnosis of OB in favor of OS,[4,5,7,10,31,34,38,41] cannot be used as a reliable indicator of malignancy, as we have shown.[36]

An important feature used for differentiating OB-like OS from OB was identification of destructive permeation of surrounding tissue. Permeation is an especially important finding because some OSs have areas that are otherwise indistinguishable from OB. Unlike OB, which almost invariably has a sharp host-tumor interface, often with peripheral bony maturation,[29] OS tends to permeate between existing trabeculae with irregular extensions. Remnants of entrapped, lamellar

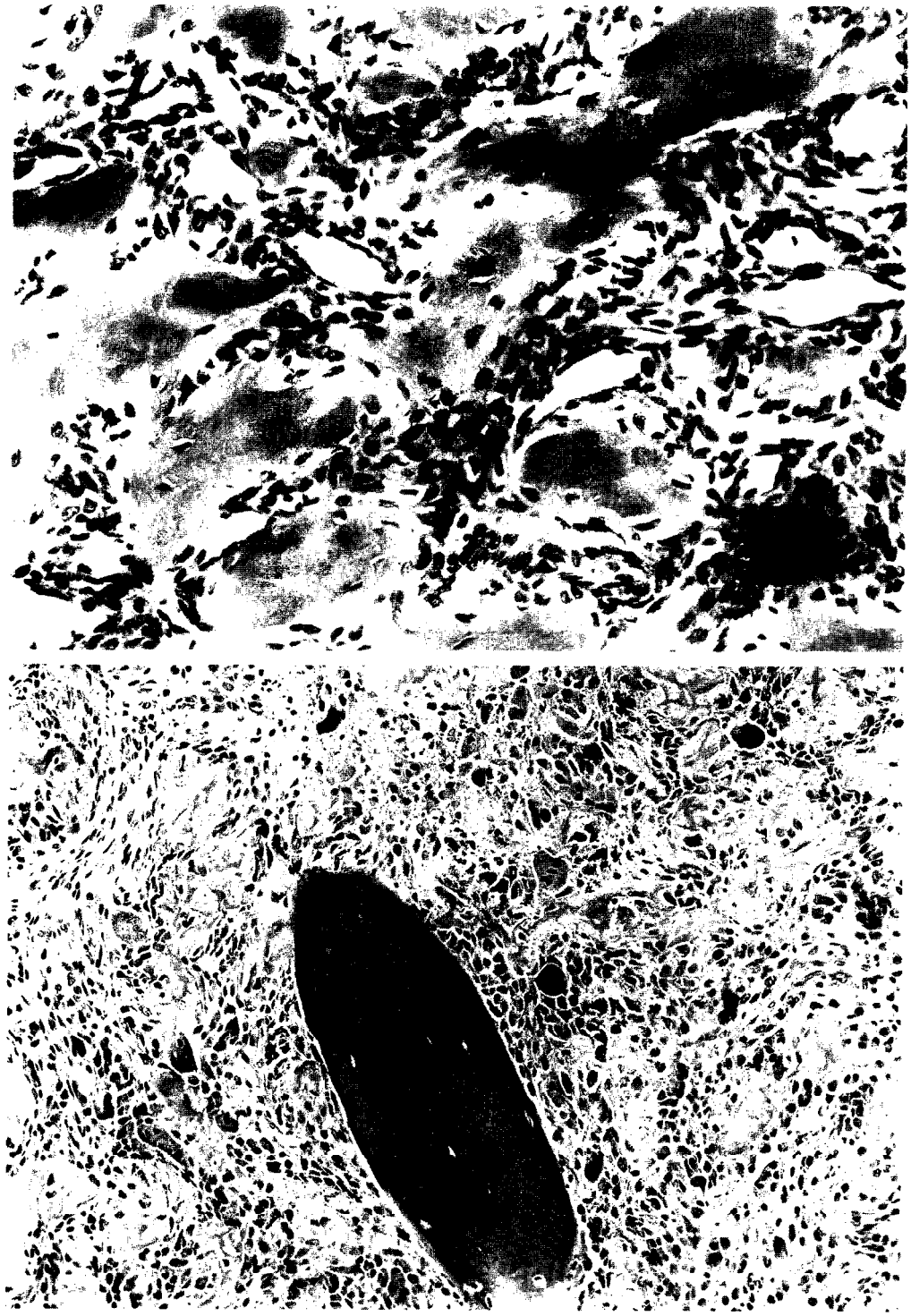

FIGURE 19. (Top) Osteoblastomalike OS shows compact arrangement of uniform cells between osteoid trabeculae. (Hematoxylin-eosin stain; magnification ×200.) (Bottom) Osteoblastomalike OS demonstrates destructive permeation evidenced by a fragment of entrapped host bone. (Hematoxylin-eosin stain; original magnification ×125.)

host bone may be seen within these tumors (Fig 19, bottom).

The radiographic appearance often helps to distinguish OS from OB; however, it is not completely reliable. A significant number of patients with OB present with features that suggest malignancy and, on rare occasions, OS may have a benign radiographic appearance.

A factor that may compound this differential diagnostic problem is that OBs on rare occasions undergo malignant transformation.[22,25-28,33] We encountered two such cases. Both tumors, well-sampled, conventional OBs initially, recurred multiple times during several years before a diagnosis of malignancy was made (Table 4). Both became high-grade OSs that ultimately metastasized. Thus, OB, like other benign bone tumors,[32,33] has the potential to undergo malignant transformation.

We addressed the problem of "aggressive OB" by identifying 30 tumors that were populated almost en-

tirely by large epithelioid osteoblasts (Table 5), an important feature of aggressive tumors, as suggested by other investigators.[9-11,15] Although the quantity of epithelioid cells needed to make a diagnosis of aggressive OB has never been clearly defined,[10,11] we chose to analyze only those cases with more than 75% epithelioid osteoblasts because smaller numbers of such cells often are found in OBs. The epithelioid osteoblast-predominant tumors tended to be more mitotically active than conventional OBs and were more likely to have a multifocal pattern; in fact, two thirds of these tumors were multifocal. We observed a wide variation in tumor size and radiographic appearance, ranging from small benign tumors to large tumors with radiographic features that suggested malignancy.

Although some OBs with a predominant epithelioid cell population do indeed pursue an aggressive clinical course, most do not. The radiographic and clinical findings parallel those of OBs in general, and we conclude that the presence of epithelioid osteoblasts alone is not a reliable predictor of aggressive behavior. Osteoblasts in an activated state (for example, in bone remodeling) often appear epithelioid and contain prominent nucleoli. Thus, epithelioid cells in OB may represent a more immature, activated form.[1,37] We believe these epithelioid tumors should be treated like conventional OBs and not be subjected to overly aggressive surgical management.

Aggressive behavior is within the spectrum of OB. As noted, 12% of the tumors in this study had radiographic features that suggested malignancy. Most of these were conventional OBs as shown by histologic findings. It appears that aggressive behavior in OB is multifactorial. Tumor location and completeness of removal are important clinical factors. Tumors situated in the vicinity of the central neuraxis are more likely to cause morbidity and mortality and are harder to remove completely.

Histopathologic features alone were not a reliable predictor of aggressiveness. We did find, however, that the presence of secondary ABC was sometimes associated with rapid, destructive growth, as often is found in primary ABCs.

Focal areas of chondroid differentiation had no prognostic significance, as we have reported,[36] and do not exclude a diagnosis of OB, as reported in the literature.[5,7,10,30,31,34,38] The presence of spiculated blue bone or foci of fine, lacelike osteoid also appears to have no prognostic significance.

Scattered large, bizarre osteoblasts are not uncommon in OB. The dark, smudgy chromatin seen in such cells probably represents a degenerative change, as was first reported by Mirra et al.[8] In rare instances, when these bizarre cells become numerous a tumor may appear pseudosarcomatous (Fig 16) and be mistaken for an OS.

A multifocal pattern (that is, the presence of more than one nidus within a single area of tumefaction) is a well-known phenomenon in OB, which was recognized as early as 1932 in Jaffe's original description.[1,4,7,34,37] Forty-three tumors (14%) in our study were multifocal, including four tumors that became multifocal after recurrence. We observed a tendency for these multifocal tumors to contain epithelioid osteoblasts. This association was responsible for a distinctive histologic pattern (Fig 17, bottom), the "epithelioid-multifocal" OB. Although there appears to be no clinical significance, distinguishing this variant of OB from OS may sometimes be difficult because it mimics permeation.

In summary, we present the clinical, radiographic, and pathologic findings from a large series of OBs. We characterize OB as a benign bone tumor with a potential for progressive (sometimes aggressive) growth, for local recurrence (16% to 21%), and, rarely, for malignant transformation. We believe that distinguishing OB from OS is one of the most challenging and important problems in orthopedic pathology and that it is sometimes impossible. The presence of destructive permeation appears to be the most helpful finding.

We addressed the question of aggressiveness in OB and were unable to identify any single histologic feature that could reliably predict aggressive behavior. We conclude that aggressive behavior in OB represents a clinical rather than a clinicopathologic entity. We agree with Dorfman and Weiss[10] that rare tumors exist with histologic and radiographic features that straddle the border between OB and OS, and that most of these probably represent OB-like OSs. Yet, given the rarity of such borderline tumors and the serious problem of distinguishing OB from OS, a diagnosis of "aggressive OB" seems precarious.

Acknowledgment. The authors thank the hundreds of physicians who provided the material and clinical information to make this study possible.

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