Original Article doi: 10.5146/tjpath.2014.01293

Cystic Bone Lesions: Histopathological Spectrum and Diagnostic Challenges

Kemiğin Kistik Lezyonları: Histopatolojik Spektrum ve Tanısal Güçlükler

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ABSTRACT

Objective: Bone cysts are benign lesions occurring in any bone, regardless of age. They are often asymptomatic but may cause pain, swelling, fractures, and local recurrence and may be confused with other bone lesions.

Material and Method: We retrospectively re-evaluated 143 patients diagnosed with aneurysmal bone cyst (n=98, 68.5%), solitary bone cysts (n=17 11.9%), pseudocyst (n=10.7%), intraosseous ganglion (n=3, 2.1%), hydatid cyst (n=2; 1.4), epidermoid cyst (n=1, 0.7%) and cysts demonstrating "mixed" aneurysmal-solitary bone cyst histology (n=12, 8.4%), and compared them with nonparametric tests.

Results: Aneurysmal bone cyst, solitary bone cysts and mixed cysts were frequently seen in the first two decades of life while the others occurred after the fourth decade. Aneurysmal bone cysts, intraosseous ganglion and pseudocysts were more common in women contrary to solitary bone cyst and mixed cysts (the female/male ratio was 1.22, 2 and 1.5 versus 0.7 and 0.5, respectively). Aneurysmal bone cyst, solitary bone cysts and "mixed" cysts were mostly seen in long bones, predominantly the femur, while epidermoid, hydatid and pseudocysts were all seen in flat bones like the vertebra, pelvis and mandible (p=0.001, chi-square). Repeat biopsies were performed in 19 cases (13.3%), 84.2% of which were aneurysmal bone cyst (5 conventional, 9 solid, 1 secondary and 1 subperiosteal) and three (15.8%) were mixed cysts (p=0.02, chi-square). Notably, some of them were located in inaccessible areas of pelvis (n=3), femur (n=3) and maxilla (n=2).

Conclusion: The most common and challenging intraosseous cysts are aneurysmal bone cysts, particularly the "solid" variant. The "mixed" aneurysmal-solitary bone cyst "subgroup" requires further research with larger series to be defined more thoroughly.

Key Words: Bone cysts, Aneurysmal bone cyst, Solitary bone cyst, Cyst hydatid, Histopathology

ÖZ

Amaç: Kemik kistleri, her yaşta ve kemikte görülebilen benign lezyonlardır. Sıklıkla asemptomatiktirler, ancak ağrı, şişlik, kırık ve lokal nüks yapabilir, diğer kemik lezyonlarıyla karıştırılabilirler.

Gereç ve Yöntem: Çalışmamızda 98'i (%68,5) anevrizmal kemik kisti; 17'si (%11,9) soliter kemik kisti; 12'si (%8,4) "mikst" anevrizmal kemik kisti-soliter kemik kisti histolojisi gösteren; 10'u (%7) psödokist, 3'ü (%2,1) intraosseöz ganglion, 2'si (%1,4) kist hidatik, 1'i (%0,7) epidermoid kisti tanısı almış; toplam 143 olgu geriye dönük olarak değerlendirilmiş, klinikopatolojik veriler nonparametrik testlerle karşılaştırılmış, bulgular histopatolojik tanı güçlükleri açısından tartışılmıştır.

Bulgular: Anevrizmal kemik kisti, soliter kemik kisti ve mikst kistler ilk iki dekatta; diğerleri dördüncü dekaddan sonra görülmektedir. Anevrizmal kemik kisti, intraosseöz ganglion ve psödokistler kadınlarda; soliter kemik kisti ve mikst kistler ise erkeklerde daha sık görülmektedir (Kadın/erkek oranı sırasıyla 1,22; 2 ve 1,5'a karşı 0,7 ve 0,5'dir) Anevrizmal kemik kisti, soliter kemik kisti ve mikst kist; femur başta olmak üzere en sık uzun kemikleri tutarken (sırasıyla %24,5, %47, %33,4;epidermoid kist, kist hidatik ve psödokistler tüm olgularda vertebra, pelvis, mandibula gibi yassı kemikleri seçmektedir (p=0,001, ki-kare). Biyopsi tekrarı yapılan 19 olgunun (%13,3); %84,2'si anevrizmal kemik kisti (5 konvansiyonel, 9 solid, 1 sekonder, 1 subperiosteal); 3'ü (%15,8) "mikst kist" dir (p=0,02, ki-kare). Bu olguların bir kısmının pelvis (n=3), femur (n=3), maksillada (n=2) zor ulaşılan alanlarda yerleştiği dikkati çekmiştir.

Sonuç: İntraosseöz kistler içerisinde en sık görülen, aynı zamanda en çok ayırıcı tanı güçlüğü yaratan lezyon solid varyantı başta olmak üzere anevrizmal kemik kistidir. Mikst anevrizmal kemik kisti-soliter kemik kisti olgu grubu iyi tanımlanmamış bir grup olup daha geniş serilerle araştırılmalıdır.

Anahtar Sözcükler: Kemik kistleri, Anevrizmal kemik kisti, Soliter kemik kisti, Kist hidatik, Histopatoloji

(Turk Patoloji Derg 2015, 31:95-103)

Received : 18.10.2014 **Accepted :** 09.11.2014

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INTRODUCTION

Bone cysts are "tumor-like" lesions appearing as cavities with variable fluid component. They may develop as solitary or multiple masses. The most common bone cysts are solitary (simple, unicameral) bone cyst (SBC) and aneurysmal bone cysts (ABC). Epidermoid cysts, intraosseous ganglion cysts and subchondral cysts are rarely seen (1). Cystic lesions of bone, particularly when a solid component is predominant, may resemble tumors or they may behave similar to a bone tumor. Thus, both SBC and ABC have been discussed within "tumors of undefined neoplastic nature" category in the World Health Organization (WHO) 2013 classification while SBC has been classified as "benign", and ABC has been classified in the "intermediate (locally aggressive)" (2) group. Accurate diagnosis of bone cysts is not only essential for their differential diagnosis with malignant tumors, but also to allow an effective follow-up program. However, one can experience diagnostic challenges, particularly when evaluating needle biopsies. In this study, we reviewed the cases diagnosed with cystic bone lesions and discussed the diagnostic difficulties.

MATERIAL and METHODS

Biopsy, curettage and/or resection specimens of patients operated between 2000 and 2010 with a clinical "bone cyst" diagnosis were retrospectively re-evaluated and 143 patients whose diagnoses were confirmed histopathologically were included in the study.

Ten cases with radiologically defined intraosseous cyst formation, i.e. following fracture healing or prosthetic surgery, were also covered in the study and categorized as reparative "pseudocyst". Odontogenic cysts of the jaw and subchondral cysts that developed secondary to degenerative joint disease were excluded.

Lesions with predominantly fibrous proliferation containing varying amounts of giant cells, reactive osteoid formation and small aneurysmal cavities and radiologically with an osteolytic appearance were defined as "solid ABC" (2, 3). "Subperiosteal ABC" was diagnosed based on radiological findings if no periosteal or cortical tissue were present in tissue samples. ABCs accompanying another lesion in the initial and/or follow-up biopsy were considered as "secondary ABC".

On retrospective evaluation, 12 cases (8.4%) were found to exhibit both ABC features (blood filled spaces separated by giant cell bearing fibrous septa) and SBC features (cyst with inconspicuous lining and amorph cementum-like fibrinoid deposits) histopathologically in either their initial or follow-up biopsies. Those cases were re-categorized as "mixed ABC-SBC". Results were compared statistically using nonparametric tests via a PC based program, SPSS version 13.0.

RESULTS

Age, gender and location distributions for cyst types have been shown in Table I. More than half of the patients (n=75; 54.1%) were female. The median age was 18±14.56 (Range: 3-73) years.

Ninety-eight cases (68.5%) were diagnosed with ABC (Figure 1, 2A-C), 17 cases with SBCs (11.9%) (Figure 3A-D), two cases (1.4%) with hydatid cysts (Figure 4A,B), and one case (0.7%) with epidermoid cyst (Figure 4C). Also, 10 patients (7%) were categorized as pseudocyst (Figure 4D), and 3 cases (2.1%) were considered intraosseous ganglion. Within the ABC group, 24 cases (24.5%) were secondary ABCs, 18 (%18.4) were solid ABC and 5 were (%5.1) subperiosteal ABC. The most common accompanying entity for a secondary ABC was giant cell tumor (GCT) (6.3%, n=9) (Table II). Examples for radiological images have been shown in Figure 5A-D.

ABCs, epidermoid cyst, intraosseous ganglion and pseudocysts tended to be seen in women, whereas SBCs and mixed ABC-SBCs were more common in men (Table I). However, the difference was not statistically significant.

Most lesions were located in the femur (25.9%, n=37), tibia (18.2%; n=26) and pelvis (11.9%; n=17) (Figure 6), regardless of the diagnosis. The overall rate of non-axial lesions was 37.8% (n=54). The femur was the most common location for ABCs, SBCs and mixed ABC-SBCs (24.5%, 47%, 33.4%, respectively; p=0,001, χ^2). Epidermoid cyst, hydatid cysts and pseudocysts were located in flat bones such as the vertebra, pelvic bones and mandible (Table I) (p=0.001, χ^2). ABCs, SBCs and mixed ABC-SBCs were more common in the first two decades of life and other

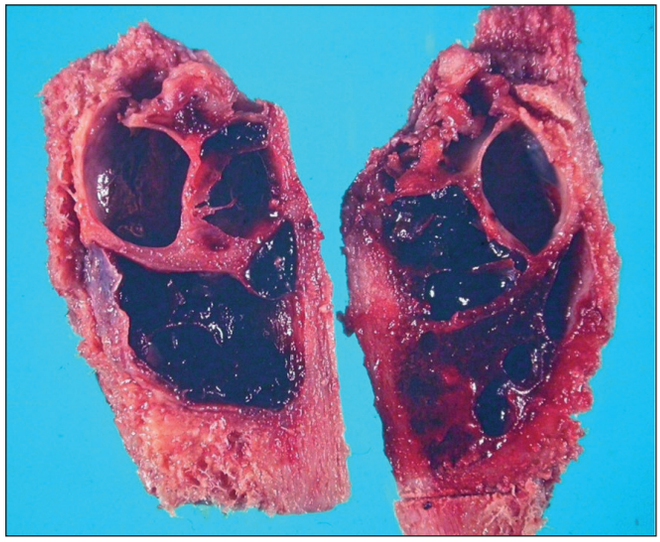


Figure 1: Gross image of aneurysmal bone cyst (ABC) demonstrating cavities filled with blood in different sizes and separated by septa.

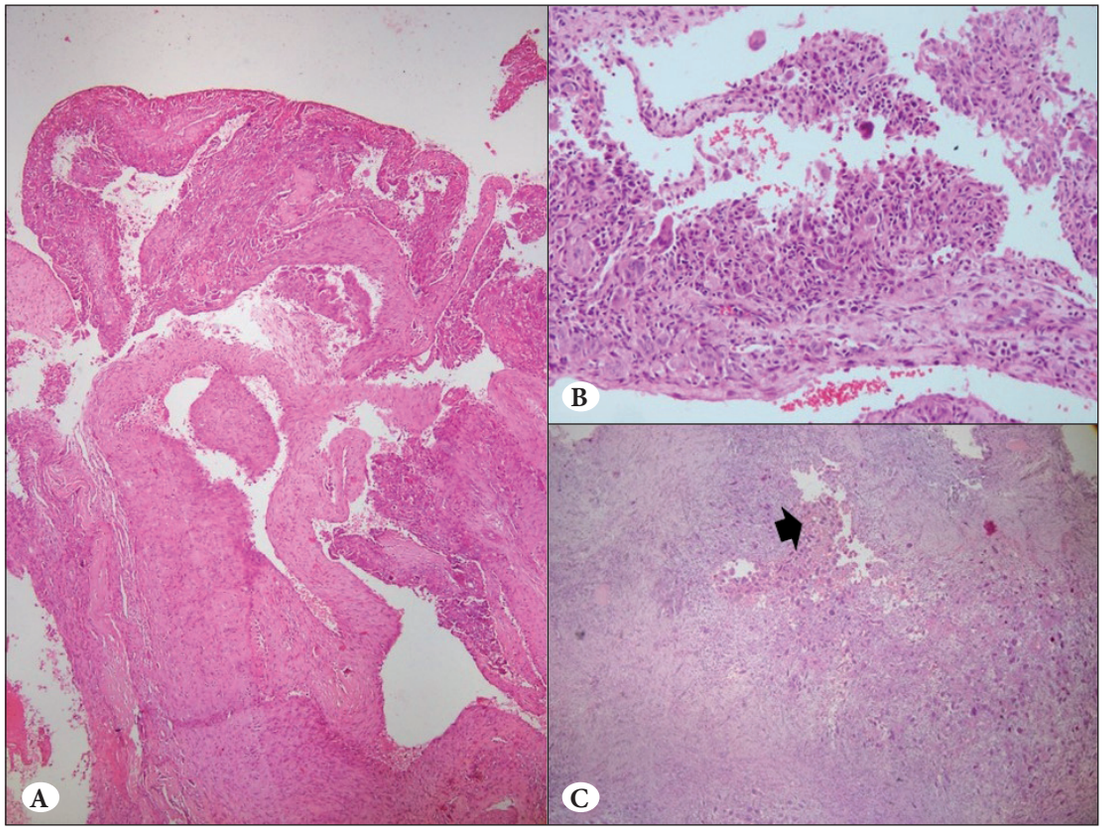


Figure 2: Aneurysmal bone cyst (ABC). **A)** Cystic spaces filled with blood and separated by fibrous septa (H&E; x100), **B)** Fibrous septa containing giant cells, hemosiderin-laden macrophages and osteoid (H&E; x200), **C)** "Solid ABC", a small cystic component is present (arrow) and giant cells tend to gather in hemorrhagic areas (H&E; x100).

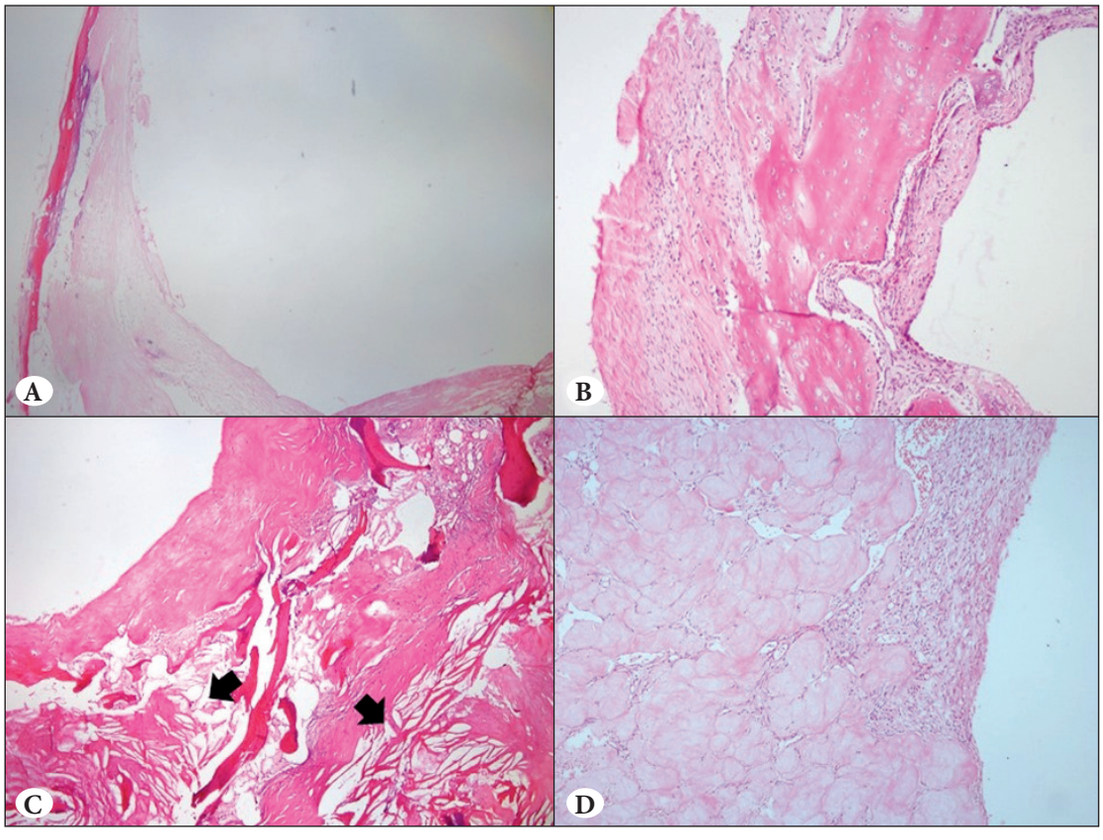


Figure 3: Solitary bone cyst (SBC). **A)** Thin-walled (generally unilocular) cyst filled with serous fluid (H&E; x100), **B)** One-layer mesothelium-like epithelium lining the thin cyst wall, (H&E; x200), **C)** Cholesterol deposition on the cyst wall (short arrows) (H&E; x200) **D)** "Amorphous" pink, fibrinoid substance of SBC (H&E; x100).

Table I: Gender, age and location distributions according to cyst types

	n	(%)	Gender	Age (Median±SD)	Location (%)
ABC	98	68.5	44 M. 54 F	18±13.5 (3-73 yrs)	Femur (24.5%), tibia (20.4%), pelvis (13.3%), vertebra (10.2%), humerus (5.1%), head bones and clavicula (4.1% each), radius. fibula and costa (3.1% each), mandible. maxilla and hand (2% each), ulna. calcaneus and scapula (1% each)
SBC	17	11.9	10 M. 7 F	10±14.0 (3-50 yrs)	Femur (47.1%), humerus (35.3%), tibia (11.8%), pelvis (5.9%)
Mixed ABC-SBC	12	8.4	8 M. 4F	12±10.11 (3-43 yrs)	Femur (33.3%), humerus (16.7%), tibia (16.7%), pelvis. head bones. clavicula and calcaneus (8.3% each)
Pseudocyst	10	7.0	4 M. 6F	32.5±14.65 (10-52 yrs)	Vertebra (20%), mandible (20%), femur (10%), tibia (10%), head bones (10%), radius (10%), maxilla (10%), ulna (10%)
Intraosseous ganglion	3	2.1	1 M. 2F	45±3 (43-49 yrs)	Tibia (33.3%), fibula (33.3%), talus (33.3%)
Hydatid Cyst	2	1.4	1 M. 1F	39.5 ± 0.7 (39-40 yrs)	Pelvis (100%)
Epidermoid Cyst	1	0.7	1F	65 yrs	Vertebra (100%)

ABC: Aneurysmal bone cyst, **SBC:** Solitary bone cyst.

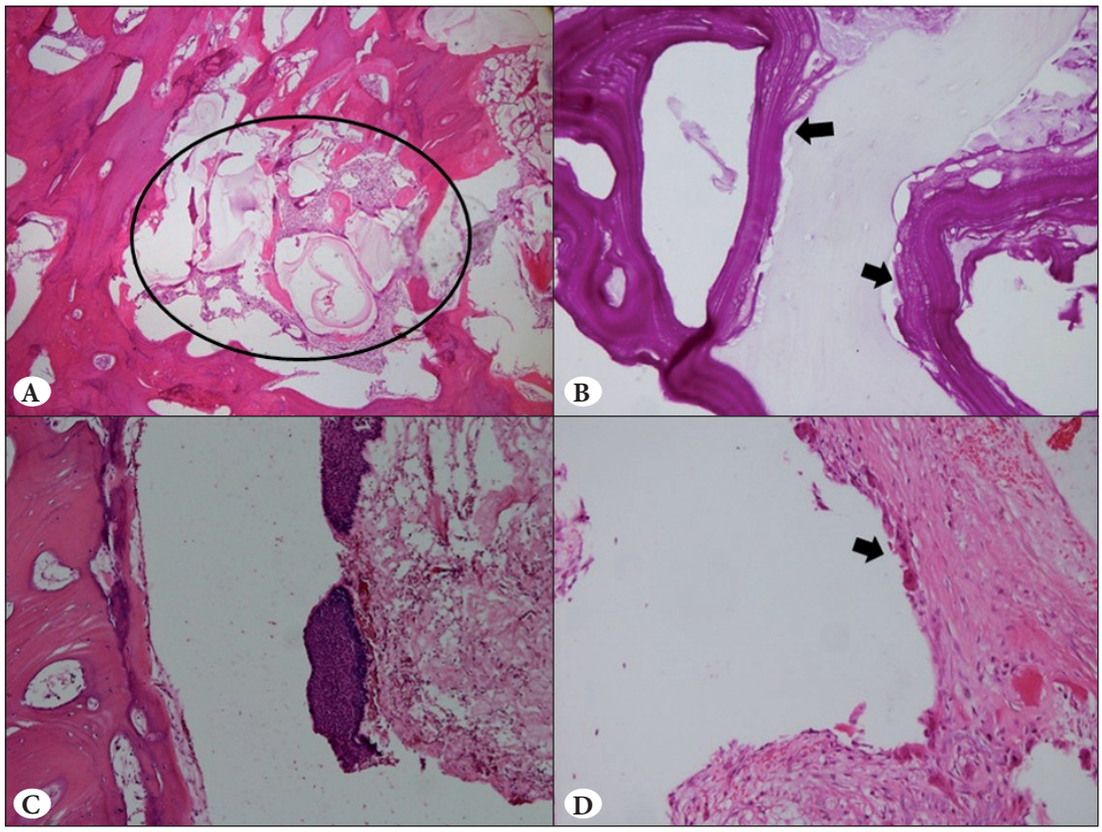


Figure 4: Other cysts. **A)** Cuticular membranes of hydatid cyst between bone trabeculae (in circle) (H&E; x100), **B)** Cuticular membranes of hydatid cyst (arrows) and bone trabecula in the middle (PAS; x200), **C)** Epidermoid cyst, with squamous epithelium on the wall (H&E; x200), **D)** Pseudocyst; periprosthetic tissue, synovium-like lining with or without one-layered epithelium and scattered giant cells (arrow) (H&E; x200).

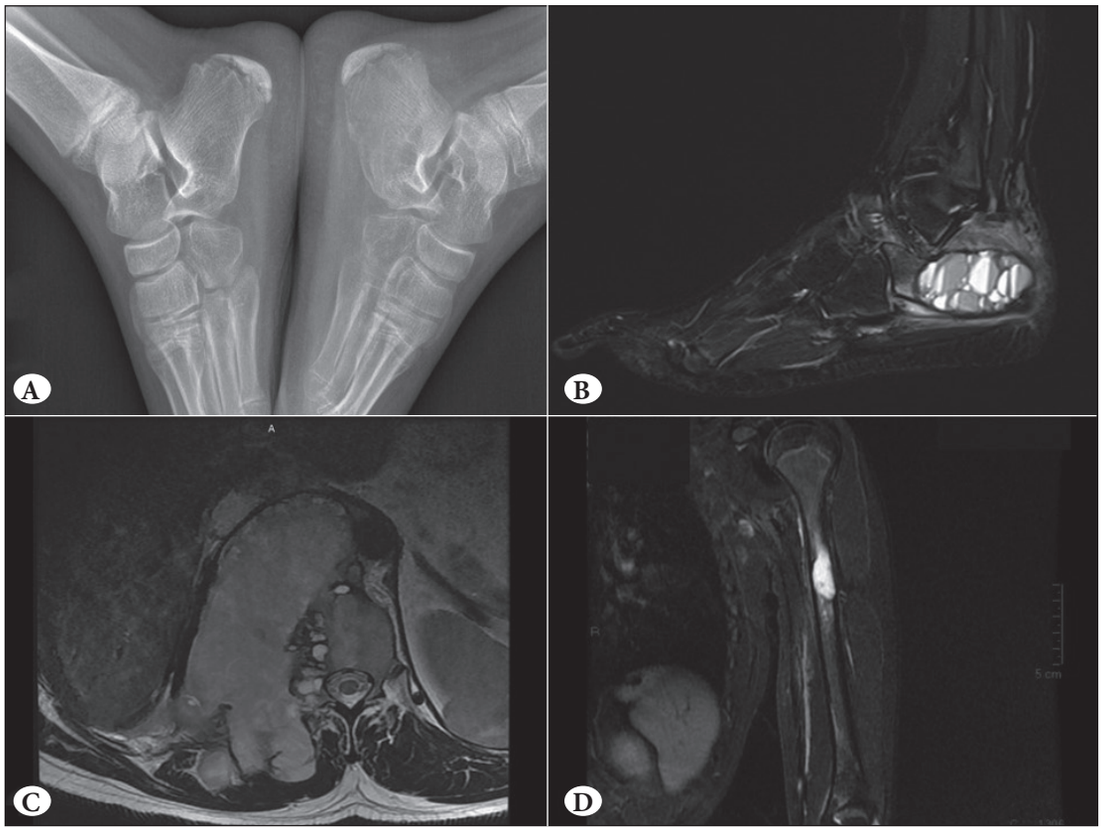


Figure 5: Examples of radiological images. **A)** Minimal expansive lytic lesion in calcaneus, left foot, plain radiography, **B)** Fluid-fluid level in a cystic lesion, consistent with aneurysmal bone cyst, in calcaneus, magnetic resonance imaging (MRI), STIR sequence, sagittal view, **C)** Hyperintense cystic lesion consistent with simple bone cyst located in diaphysis of humerus, MRI, STIR sequence, coronal view, **D)** Paravertebral hydatid cyst at T11-L1 level. Destruction and compression is remarkable on T12 corpus. MRI, T2 weighted axial view.

Table II: Distribution of aneurysmal bone cyst (ABC) cases

		n	%
Conventional ABC		51	52
Solid ABCS		18	18.4
Secondary ABCs	Accompanying lesion	24	24.5
	Giant cell tumor	9	6.3
	Fibrous dysplasia	6	4.2
	Chondroblastoma	5	3.5
	Osteofibrous dysplasia	1	0.7
	Osteoblastoma	3	2.1
	Osteosarcoma	1	0.7
Subperiosteal ABCs		5	5.1
Total		**98**	**100.0**

ABCs: Aneurysmal bone cysts.

cysts were seen after the fourth decade (p=0.000; χ^2) (Figure 7). Nineteen patients (13.28%) underwent a second needle biopsy or open biopsy because of diagnostic difficulties. Among these, 16 (84,2%) had ABC, and 3 (15,8%) had mixed ABC-SBCs. Sixteen ABC cases included 5 (26.3%) conventional ABCs, 9 (47.4%) solid ABCs and 1 (5.3%) secondary and 1 (5.3%) subperiosteal ABCs. The patient, categorized as secondary ABC after repeat biopsy had chondroblastoma in the repeat biopsy. The reason for the repeat biopsy was associated with the diagnosis (p=0.02, χ^2). There was no significant correlation between repeat biopsy and age, gender and location; however, some lesions were located in inaccessible areas of the pelvis (n= 3), femur (n=3), maxilla (n=2) and fibula (n=1). The percentage of those cases among all cases located in the mandible, maxilla and fibula were 50%, 66,7% and 25%, respectively.

DISCUSSION

The incidence of cystic lesions of the bone is not well known. This is partly due to their asymptomatic disease course in most cases, being diagnosed either incidentally or as a result of a complication such as fracture. Some cysts can only truly be diagnosed and categorized histopathologically (e.g. epidermoid cyst) and are not biopsied in most cases as they exhibit nonspecific features which can be regarded as a consequence of post-traumatic or iatrogenic processes clinically and radiologically, therefore not creating any necessity for a biopsy (4). Nevertheless, it would not be a false statement to accept ABCs and SBCs as the most frequent bone cysts (2). The most common symptom of bone cysts is swelling (2, 4, 5), which is generally recognized a long time after the onset or is neglected by the patient.

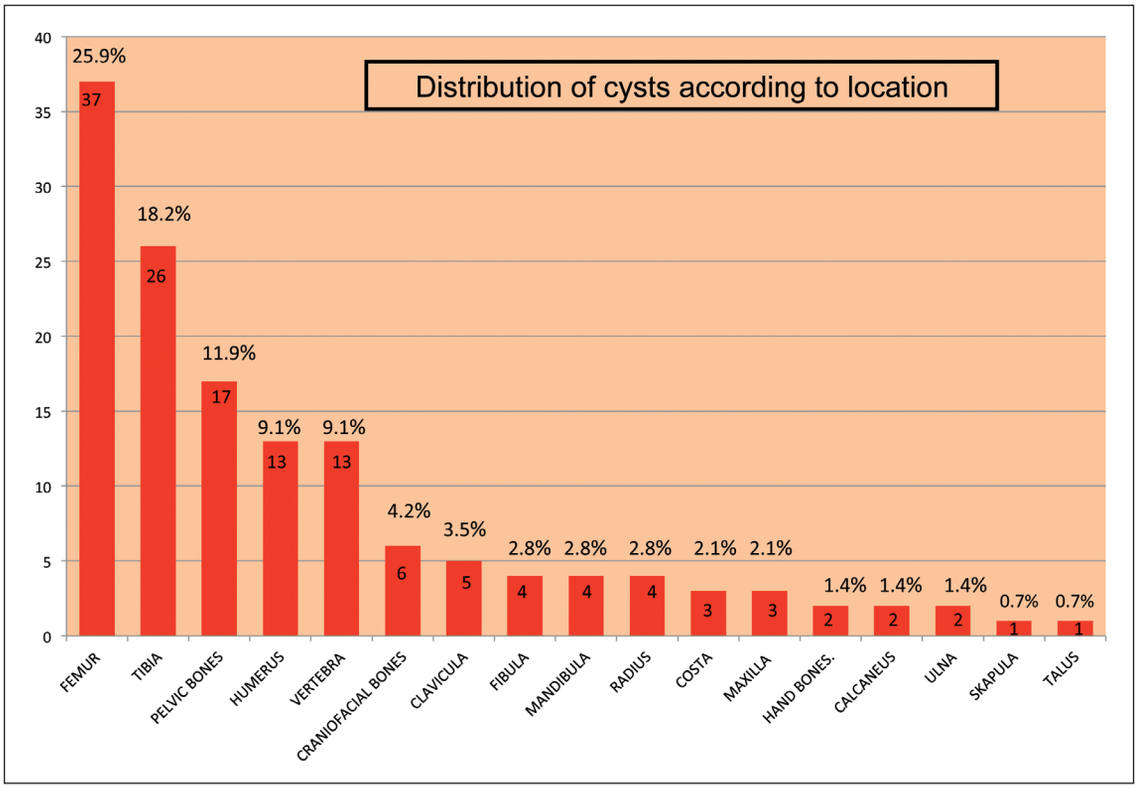
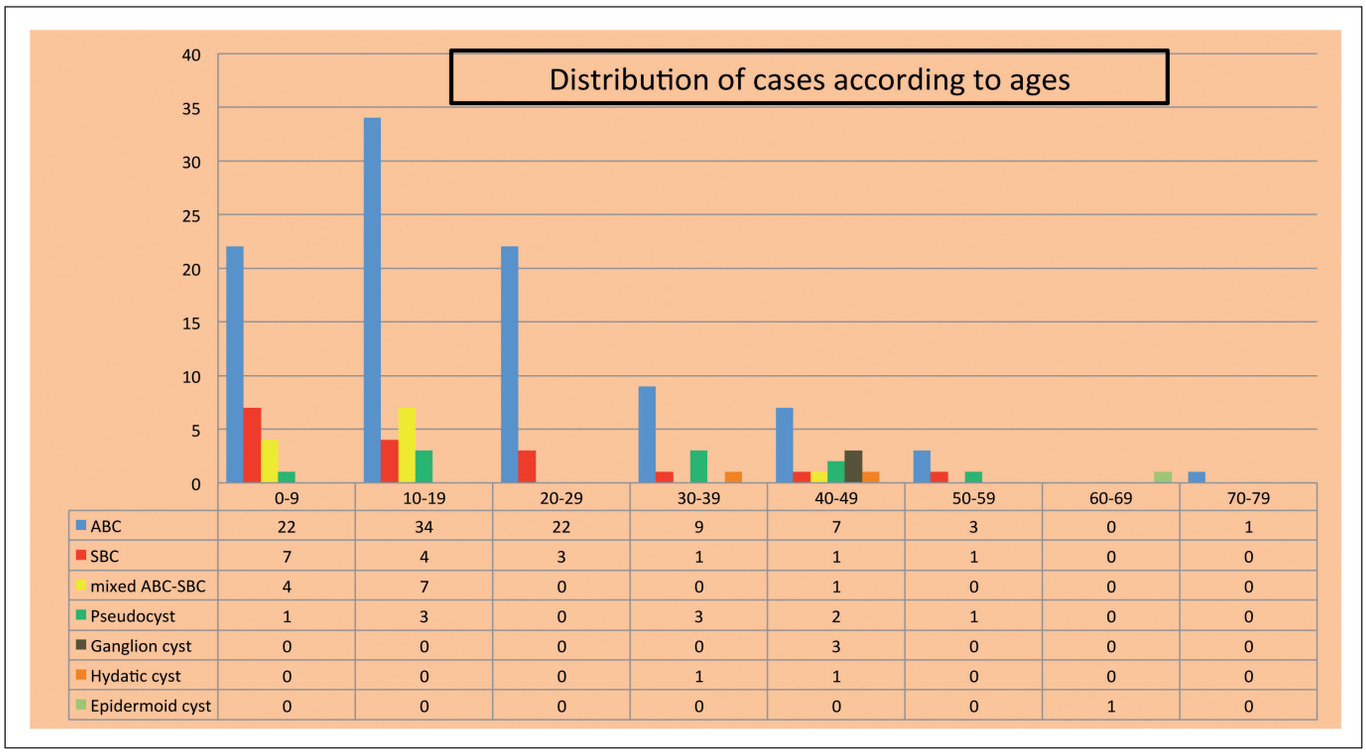


Figure 6: Distribution of the cysts according to location.



	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
ABC	22	34	22	9	7	3	0	1
SBC	7	4	3	1	1	1	0	0
mixed ABC-SBC	4	7	0	0	1	0	0	0
Pseudocyst	1	3	0	3	2	1	0	0
Ganglion cyst	0	0	0	0	3	0	0	0
Hydatic cyst	0	0	0	1	1	0	0	0
Epidermoid cyst	0	0	0	0	0	0	1	0

Figure 7: Distribution of cases according to ages. Note the wide age range of ABC.

Therefore, the most common complaints are generally pain and/or fracture at the site of the bone cyst (2). Paraparesia, hypoesthesia and sphincter dysfunction may also occur due to compression to the nerves in spinal ABC cases (6).

ABCs, SBCs and mixed ABC-SBCs were found to be located in long bones, especially in the femur, in our study group. On the contrary, epidermoid cyst, hydatid cyst and pseudocysts appeared to tend to occur in flat bones such as the vertebra, pelvic bones and mandible. ABCs and SBCs are more common in the first two decades of life but particularly ABCs may occur in any bone regardless of age. We also observed that although the age distribution is variable, ABCs, SBCs and mixed ABC-SBCs were more frequent in the first and second decade while the other cysts were more frequent after the third decade. The age range varied the most for ABCs; between the first decade and the eighth decade of life. Although it would be wise to interpret this observation carefully, considering that 70% of the patients included in the study had ABCs, it is consistent with previous studies (7).

ABC is characterized by cystic spaces filled with blood and separated by fibrous septa containing osteoclast-like giant cells (2). It was first described by Jaffe and Lichtenstein (8,9). However, its neoplastic origin and biological behavior are still controversial, even after 60 years. ABC is a well-circumscribed, cystic, expansive and radiolucent lesion and it can easily be diagnosed with the presence of characteristic fluid-fluid levels and fibrous septa on magnetic resonance imaging (MRI) (2). The main diagnostic challenge for ABC is the possibility for misdiagnosis of telangiectatic osteosarcoma both on histological and radiological evaluation (10). Repeat biopsy has been performed in 5 of our patients because of this possibility. Cellular atypia, atypical and especially tripolar-tetrapolar mitoses, and the presence of irregular, lace-like osteoid are the most important features that favor telangiectatic osteosarcoma (2, 11). However, one should bear in mind that osteoid formation may be prominent in ABC as well. Care must also be taken not to confuse the "polymorphism" caused by different cell types present in ABC with "pleomorphism" of tumor cells in osteosarcoma. In our ABC group, 18.4% were defined as solid ABC, representing 47.4% of repeat biopsies. Solid ABC may contain small ABC areas but fibrous proliferation is more prominent and it may resemble "giant cell reparative granuloma" of the jaw and "Brown tumor of hyperparathyroidism" with nonspecific features such as scarce giant cells, hemorrhagic areas and reactive osteoid formation (3). Similar findings may also be seen in the periphery of fibroosseous lesions and nonossifying fibroma. Thus, differential difficulties may occur when evaluating cases that do not have small cystic areas or in cases without a clinical and/or radiological suspicion. Clinical and radiological data are also important in the diagnosis of secondary ABCs. It has been reported that there may be an underlying pathology, especially GCT, in 19-39% of ABCs (12). There were 24 (24.5%) secondary ABCs among our ABC cases and the most common accompanying entity was found to be GCT, in consistence with previous studies. However, accompanying entities were quite variable and included chondroblastoma and osteosarcoma. The incidence of secondary ABCs accompanying fibrous dysplasia has been reported to be about 10% (13). Only an ABC appearance was present in the first biopsy sample of our chondroblastoma case, while a chondroblastoma diagnosis had been made according to the repeat biopsy performed due to a radiological suspicion. This was a very demonstrative case showing the importance of clinical and radiological data in diagnosis. Recent cytogenetic studies have shown that spindle cells which are the neoplastic component of primary ABC have USP6 (ubiquitin specific peptidase 6/Tre-2) gene rearrangement, in contrast to secondary ABCs (2). Unfortunately, no histological clue has been defined to distinguish these spindle cells from the usual fibroblasts and myofibroblasts or secondary ABC from primary ABC. Therefore, it is essential to be oriented to the biopsy site and repeat biopsy will be a critical step for the diagnosis when needed.

SBC or unicameral bone cyst is a unilocular cyst with one-layer mesothelium-like epithelium lining the thin cyst wall, and reactive bone formation, scattered giant cells and occasionally cholesterol clefts are seen on the cyst wall. Amorphous cement-like fibrin depositions are considered important clues for the diagnosis. (2). SBC generally occurs in the first two decades and in men. The humerus, femur and tibia are the common locations. The distribution of age, gender and location of our SBCs were similar to those previously reported (1, 2), in spite of a slight femoral predominance in our series. Patients are generally asymptomatic unless fractures occur. Radiologically, it has a well-circumscribed and lytic appearance and the diagnosis can easily be made either radiologically or histopathologically in uncomplicated lesions (14). However, an extremely thin cyst wall may cause fragmentation and adhesion of the cyst wall during the biopsy procedure, resulting in diagnostic difficulties. Moreover, cement-like fibrinoid material, which is an important histopathological feature for the diagnosis, cannot be demonstrated in every tissue sample.

We also recognized that 12 cases (8.4%) exhibiting typical SBC features also had ABC-consistent areas either in the same biopsy sample (n=5) or in the repeat biopsy (n=7). This finding is not a common or conventional feature. It is reported that cyst fluid may be hemorrhagic due to fractures (2), however it is not known whether this can mimic ABC or not. Of 12 cases in our series, only one case showed changes due to fracture but history of fracture and/

or trauma or pre-referral radiological images could not be obtained for the remaining patients. Hence, it is not possible to eliminate a SBC complicated by hemorrhage and hematoma organization mimicking an ABC. Nonetheless, the fact that distribution of age, gender and location were more suitable for SBC and the presence of small ABC-like areas similar to foci seen in secondary ABCs suggested that ABC components were present as secondary findings.

The cysts defined as "pseudocyts" are not also conventionally described cysts. They were included in the study group as they were radiologically defined as cysts, differed from subchondral bone cysts as they were unrelated to osteoarthritis. and also appeared as a "cyst" histologically. There are reports on such cysts developed in periprosthetic tissues or following a history of fracture or minor trauma (15). Pseudocysts resemble synovial cysts with synovium-like lining with or without one-layered epithelium. Foreign body reaction was also observed in some cyst walls, in consistence with previous reports (16). Three patients who had a periprosthetic pseudocyts were older than patients who had post-fracture pseudo-cysts.

Cysts exhibiting morphology similar to ganglion cysts of soft tissue in the absence of history of fracture or prosthesis were considered as "intraosseous ganglion cyst" and those cases were also elderly patients. Synonyms such as ganglion cyst, inclusion cyst etc. can be used for intraosseous ganglion cysts. Its histological difference from subchondral cysts seen in degenerative joint disease or so-called pseudocyst herein and whether subchondral cysts can or cannot be assessed as ganglion cysts are controversial (17). However, a synovium-like lining was demonstrated in our cases while other features seen in degenerative subchondral cysts such as fibrosis and fat necrosis in the surrounding bone marrow, osteonecrosis and chondronecrosis were not present (18). The necessity for removal and follow-up of these lesions is controversial as well.

Hydatid cysts and epidermoid cysts can be recognized more easily due to their usual histopathological features (5,19). However, diagnostic difficulties may occur in several occasions, especially while evaluating needle biopsies as desquamation of epithelium in epidermoid cysts, faint staining of cuticular membrane in hydatid cysts, very small or fragmented cuticular membranes, especially for alveolar hydatid cysts. It is also essential to know that epidermoid cyst was located inside the bone to distinguish from the soft tissue counterpart.

In conclusion, biopsy and/or curettage samples of 143 patients were retrospectively re-evaluated in this study. The demographic findings were consistent with the literature. ABCs were the most common intraosseous cysts, also presenting as the most challenging cysts causing diagnostic difficulties. For heterogeneous lesions with small and inadequate biopsy samples, clinical and radiological correlation is especially required. The most frequent reason for repeat biopsy was to distinguish solid ABC and telangiectatic osteosarcoma in clinically and radiologically suspected cases. Histopathological evaluation leads to the diagnosis in most cases. However, differential diagnosis between telangiectatic osteosarcoma, giant cell tumor of the bone, reparative granuloma, and brown tumor of hyperparathyroidism can be difficult by histopathological evaluation alone when evaluating small and/or inadequate needle biopsies. Clinical and radiological correlation is valuable for cystic lesions of bone, similar to other bone lesions.

There is no reliable data on the incidence and types of bone tumors in Turkey. However, in a previous review by Yuceturk et al, 114 ABCs, 36 SBCs and 8 hydatid cysts have been reported among 5658 patients diagnosed with bone tumors in a single center in 20 years period. Other studies focus on only one type of bone cysts (21,22). In this context, this study represents one of the largest series with bone cysts in Turkey and, to best of our knowledge, is the only one focusing on their histopathological features.

To our knowledge, there is also very few data regarding the so-called "mixed ABC-SBC" group showing features of both ABCs and SBCs. Whether they represent a secondary ABC that developed in patients with underlying/accompanying SBC or not is not known. Further research in large patient groups is required to explore this entity.

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