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Original Article

Correlation between histological and ultrasonographic findings of soft tissue tumors: To verify the possibility of cell-like resolution in ultrasonography

Ching-Lan Wu [a,c], Yi-Chen Lai [a,c], Hsin-Kai Wang [a,c], Paul Chih-Hsueh Chen [b,c], Hong-Jen Chiou [a,c,d,*]

[a] *Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[c] *School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[d] *School of Medicine, National Defense Medical Center, Taipei, Taiwan, ROC*

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Abstract

Background: The purpose of this study is to test the possibility of obtained cell-like resolution in soft tissue tumors on the basis of ultrasound echotexture.

Methods: This is a prospective study consisting of 57 patients (29 females and 28 males, age range: 9−83 years, average age: 44.5 years) with palpable soft tissue mass, referred from the Departments of Orthopedics and Oncology for ultrasound (US)-guided biopsy. The study was approved by the institutional review board (IRB) of our hospital. Ultrasonographic images were recorded by still imaging in the biopsy tract in each biopsy session. Equipment included curvilinear and linear array probes. After biopsy, a radiologist and a pathologist correlated the US image and the observations regarding the histology of the tissue specimen in low-power (40 × magnification) and high-power (100−400 × magnification) fields.

Results: The histologic results included 22 benign and 35 malignant lesions. The echotexture of the soft tissue tumors correlated well with the cellular distribution and arrangement: the greater the number of cells and the more regular their arrangement as seen histologically, the greater is the hypoechogenicity on the ultrasound. The echogenicity of the soft tissue tumor also correlated well with the presence of fat cells, hemorrhage, cartilage, and osteoid tissue, all of which cause an increase in echogenicity.

Conclusion: This study showed that the echotexture of soft tissue tumors can predict some details of cellular histology.

Keywords: Histology; Soft tissue tumors; Ultrasonography

1. Introduction

Ultrasound has been widely applied in the evaluation of palpable soft tissue masses. The benefits of ultrasound are nonionizing radiation, low cost, ready applicability and availability, ability to characterize and define anatomic extent of the lesion, guiding diagnostic and therapeutic procedure or biopsy.[1−3] High-resolution ultrasonography, an emerging modern technique, has been wildly used in current clinical settings.[4−6] With regard to soft tissue lesion evaluation, high-resolution ultrasonography were highly sensitive to detect the masses presence but the specificity for histological discrimination is generally low.[7−10] Therefore, it has not proven useful for differentiating between benign and malignant conditions.[7,10,11] Actually, the ultrasonographic parameters commonly

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* Corresponding author. Dr. Hong-Jen Chiou, Department of Radiology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.

E-mail address: hjchiou@vghtpe.gov.tw (H.-J. Chiou).

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used in the evaluation of soft tissue mass to describe tumor characteristics, including echogenicity (hyper-, hypo-, and iso-), internal texture (heterogeneity or homogeneity), shape, and margins, have not been specified in many previous studies,[8,9] including ours,[12] possibly because these parameters are insufficient to reflect the complexity of the soft tissue mass. The histological constitution of the soft tissue tumor was found to vary even in tumors of the same histopathology, and studies of greater detail are needed to characterize these differences. This study was designed to correlate the details of echotexture with histology in order to obtained cellular-like resolution of ultrasonography.

2. Methods

This prospective study was approved by the IRB of our hospital. There were 57 patients (29 females and 28 males, age range: 9−83 years, average age: 44.5 years) with palpable soft tissue mass who were referred from the Orthopedics and Oncology departments for ultrasound-guided biopsy. Each soft tissue mass was scanned by gray-scale and color Doppler ultrasonography, and images were stored in the pictures archiving and communication system (PACS) system. Before biopsy, each patient was clearly explained the procedure, and the patients signed a consent form. The skin was sterilized with Betadine®, the probe was enveloped in a sterile plastic bag, and local anesthesia with 7−10 ml of 2% lidocaine was induced. Various vascular parts of the tumor were then sampled by a free-hand technique with ultrasonographic guidance. During the biopsy procedure, the needle tract was recorded by freeze-imaging at the following points: before the inner stylet was let out of the biopsy needle, when it was completely protruding at a length of 2 cm, and when the cutting needle was fired (Fig. 1, cutting image). We selected a 16-gauge semiautomatic biopsy-gun (Cardinal Health Care, Dublin, OH) with a 2-cm core length as the needle. In each mass, 2−5 cores were collected, depending on the completeness of the specimen. Each specimen was then separately stored in a formalin bottle that was properly labeled in order to enable correlation with the ultrasonographic location. After biopsy, the puncture sites were routinely checked for bleeding with color Doppler ultrasound (CDUS), and the puncture site was compressed with a sandbag for 2 h; all patients were monitored during this period. In total, 142 cores of specimen with were collected for comparison. The echotexture was variable in each stripe of the specimen. On the basis of similar echotexture, 196 segments were grouped for correlation with the histological characteristics.

The ultrasonic machines we used included the HDI 5000 system (Philips Medical Systems, Bothell, WA) with L12-5

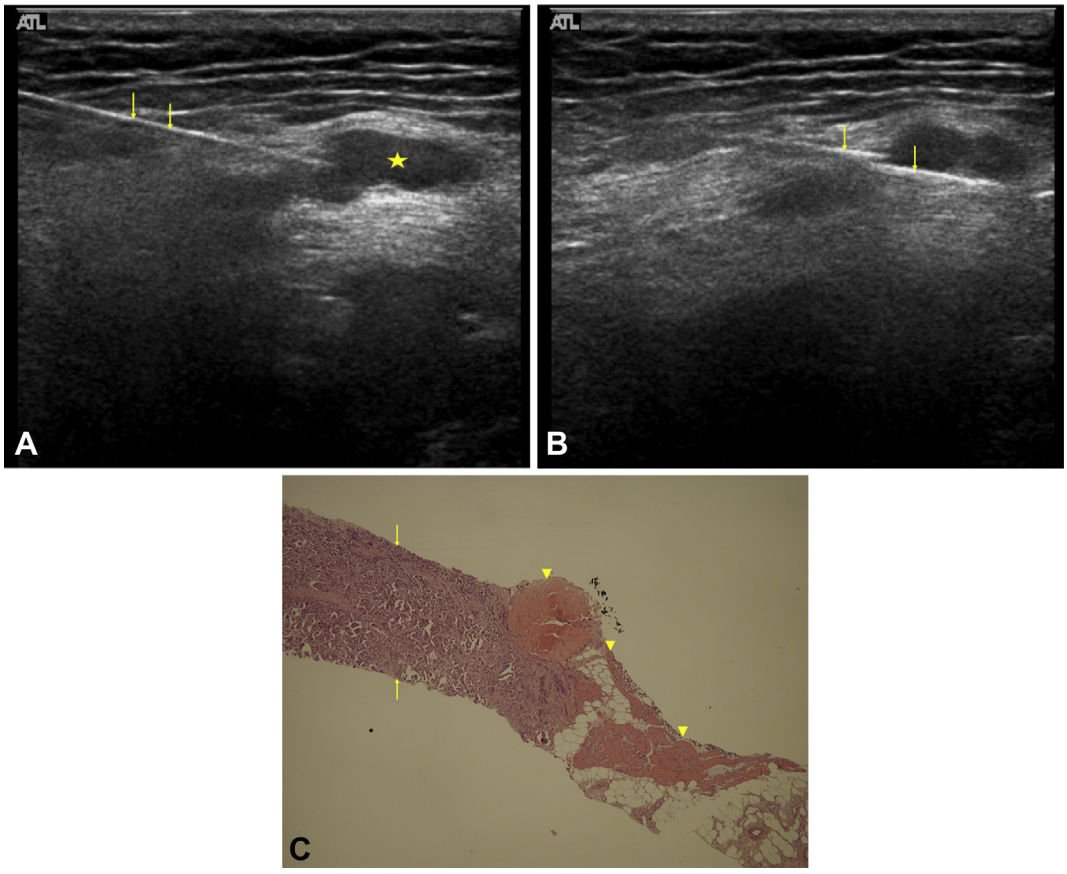

Fig. 1. A 83 y/o male patient complaint of calf nodule. (A)Gray scale ultrasound showed moderate hypoechogenicity in the tumor (asterisk) but hyperechoic in the margin. Arrows: needle (B) The needle (arrows) pass through the tumor part and hyperechoic capsule and muscle, (C) the histology showed the tumor nest (arrows) and muscle, fat, connective tissue (arrowheads).

and CL15-7 linear and C5-2 curved linear transducers; a GE Voluson 730 system (GE Healthcare, Milwaukee, WI) with RAB 2-5 and RAB 4-8 curved and SP10-16 and RSP 6-12 linear transducers.

Correlation of ultrasonographic images (with a focus on echogenicity and echotexture) and review of the core tissue specimen in low-power (40 × magnification) and high-power (100−400 × magnification) fields were performed by a radiologist and a pathologist. Echogenicity was recorded as 7 grades with respect to the surrounding tissue, such as muscle: marked, moderate, and minimal hypoechoic; isoechoic; and minimal, moderate, and marked hyperechoic. The tissues of each grade were then categorized as either homogeneous or heterogeneous according to the echotexture compared to surrounding muscle. The ultrasonic images were separately read from the PACS system by two senior sonologists (HJ C and HK W); if there was any difference in the results, they had a discussion to reach a consensus.

The histological parameters were cell type (such as small cells, large cells, simple, or multiple) and cell arrangement (such as loose, compact, or chaotic). If the cell present as longitudinal arrangement (including curve) will come with acoustic anisotropy effect.

The kappa statistic was used to measure the degree of concordance between sonographic findings and histological results, Kappa statistics of 0.21−0.40 indicate fair agreement, 0.41 to 0.60 indicates moderate agreement, 0.61 to 0.80 indicates substantial agreement and 0.81 to 1.00 indicates perfect agreement.[13]

3. Results

The histologically proven lesions comprised 22 benign (for example, granulomatous lesions, diffuse type of synovitis, giant cell tumor, myositis ossificans, fibrosis, and neurofibroma) and 35 malignant tumors (for example, metastasized tumors, synovial sarcoma, alveolar soft part sarcoma, lymphoma, myxoid liposarcoma, osteosarcoma, Ewing's sarcoma, and fibrosarcoma) (Table 1). The tumors were histologically described as capsular (layers of compact fibroblasts), having chaotically arranged cells, having loose fibroblasts in a collagen matrix, having compactly arranged cells (including clustered tumor cells, compact lymphocytes, compact clustered tumor cells with regular fibroblasts, and several fibroblasts arranged as a curve), having necrotized, having osteoid tissue, having clustered fat cells, having small vessel distribution, having small areas of hemorrhage, having minimal to moderate number of fibroblasts arranged in a curve, having alveolar tumor nests with some fibroblasts, and having chondroid tissue with myxoid component. According to cell type and arrangement, the histological type was generally categorized as a predominant single-cell type with compact arrangement, several types of tumor cells with compact arrangement, single or several tumor cell types with loose arrangement, and specific types of tumor cells (such as fat cells, calcified or osteoid tissue, vessels, fluid, and hemorrhage) with compact or loose arrangement.

Table 1
The histology and patient's number.

Histology	Patient number (subtotal)
Benign histology	
Chronic granulomatous lesion and fibrosis	8
Acute and chronic inflammation	4
Myositis ossificans, PVNS	2(4)
Neurofibroma, GCT, Chondromyxoid fibroma, fibromatosis, traumatic neuroma, ductal hyperplasia with atypia	1(6)
Total	22
Malignant histology	
Metastatic carcinoma	8
Synovial sarcoma	6
B cell lymphoma	5
Alveolar soft part sarcoma	3
Ewing sarcoma, OGS, chondrosarcoma, liposarcoma, sarcoma unclassified	2(10)
Myxofibrosarcoma, MFH and leiomyosarcoma recurrence	1(3)
Total	35

From the histological examination, we found that 17 segments contained separate fat cells, which presented as mild to moderate heterogeneous or moderate homogeneous hyperechogenicity (10 presented as moderate homogeneous hyperechogenicity) (Table 2 and Fig. 2); 33 of 38 segments contained compactly arranged tumor cells (including several tumor cells, only lymphocytes, compact clustered tumor cells with regular fibroblasts, and several fibroblasts arranged in a curve), which presented as moderate heterogeneous or homogeneous hypoechogenicity (Table 2 and Fig. 3); 15 segments contained fibrous capsules, which presented as mild to moderate heterogeneous hyperechogenicity (Table 2 and Fig. 4); 6 of 8 segments contained collagen fibers and loose fibroblasts, which presented as mild heterogeneous hypoechogenicity; 21 of 33 segments mainly contained compact tumor cells (including clustered tumor cells, compact lymphocytes, compact clustered tumor cells with regular fibroblasts, or several fibroblasts arranged in a curve) along with other kinds of cells, which presented as mild or moderate heterogeneous hypoechogenicity; 8 of 10 segments contained osteoid tissue, which presented as heterogeneous moderate to severe hyperechogenicity (Table 2 and Fig. 5); 39 of 51 segments contained mainly loose fibroblasts in a collagen matrix with few other cell types, which presented as heterogeneous mild hypo- or hyperechogenicity; 5 of 23 segments contained mixed cells with vessels, which presented as heterogeneous mild hypo- or hyperechogenicity; 6 segments contained mainly alveolar tumor nests along with some fibroblasts and other cells, which presented as heterogeneous iso- to hyperechogenicity; finally, 31 of 39 segments contained mainly mild to moderate numbers of fibroblasts along with other cell types arranged in a curve, which presented as heterogeneous moderate or minimal hypoechogenicity. All of above mentioned results were statistical significance with the p-value less than 0.05.

Table 2
Correlation between ultrasound findings and histology.

	Clustered separated fat cells (F) vs. heterogeneous mild (5H), homogeneous and heterogeneous moderate hyperechogenicity (6E and 6H). Kappa value = 0.347, P-value < 0.001		
Histology	F	Non-F	Total
Ultrasound			
5H, 6E, 6H	17	44	61
Non-5H, 6E,6H	0	135	135
	Compact arrangement of tumor cells (D) vs. homogeneous and heterogeneous moderate hypoechogenicity (2E and 2H). Kappa value = 0.592, P-value < 0.001		
Histology	D	Non-D	Total
Ultrasound			
2E, 2H	33	25	58
Non-2E, 2H	5	133	138
	Fibrous capsule (A) vs. heterogeneous mild and moderate hyperechogenicity (5H and 6H). Kappa value = 0.398, P-value < 0.001		
Histology	A	Non-A	Total
Ultrasound			
5H, 6H	15	34	49
Non-5H, 6H	0	147	147
	Osteoid tissue (O) vs. heterogeneous moderate and marked hyperechogenicity (6H and 7H). Kappa value = 0.429, P-value < 0.001		
Histology	O	Non-O	Total
Ultrasound			
6H, 7H	8	16	24
Non-6H, 7H	2	170	172
	Homogeneous moderate hypoechogenicity (2E) vs. compact arrangement of tumor cell (D). Kappa value = 0.601, P-value < 0.001		
Histology	D	Non-D	Total
Ultrasound			
2E	22	6	28
Non-2E	16	152	168
	Homogeneous moderate hyperechogenicity (6E) vs. clustered separated fat cells (F). Kappa value = 0.666, P-value < 0.001		
Histology	F	Non-F	Total
Ultrasound			
6E	10	7	17
Non-6E	2	177	179

F: clustered separated fat cells; 5H: heterogeneous mild hyperechogenicity; 6E: homogeneous moderate hyperechogenicity; 6H: heterogeneous moderate hyperechogenicity; D: compact arrangement of tumor cells; 2E: homogeneous moderate hypoechogenicity; 2H: heterogeneous moderate hypoechogenicity; A: fibrous capsule; O: osteoid tissue; 7H: heterogeneous marked hyperechogenicity.

The ultrasonographic results showed 22 of 28 segments showing homogeneous and 11 of 30 segments showing heterogeneous moderate hypoechogenicity contained compact tumor cells (Table 2); 10 of 62 segments showing heterogeneous minimal hypoechogenicity contained mainly compact tumor cells along with loose collagen fiber, a few fat cells, vessels, and mild hemorrhage; 1 segment showing heterogeneous isoechogenicity contained alveolar tumor nests with fibroblasts; 7 of 27 segments showing heterogeneous minimal hyperechogenicity contained tumor capsules; 10 of 17 segments showing homogeneous moderate hyperechogenicity contained several individual fat cells (Table 2); 2 segments showing marked heterogeneous hyperechogenicity contained osteoid tissue. All of the above findings showed statistical significance with the p-value less than 0.05.

The echotexture of the soft tissue tumors correlated with cellular distribution and arrangement observed in histological examination; the greater the number of cells and the more regular the arrangement, the greater was the hypoechogenicity (Table 2).

The echotexture of soft tissue tumor also correlated with the presence of fat cells, hemorrhage, cartilage, and osteoid tissue, all of which result in increased echogenicity. Therefore, from the echotexture of soft tissue tumors, we could predict some details of the cellular histology (Table 2).

With regarding to image reading, inter-observer and intra-observer variability assessment were not available in this study.

4. Discussion

In medical ultrasound, the transducer frequencies usually range from 2 to 15 MHz; the best axial resolution, therefore, ranges from around 100 μm to 770 μm on the basis of the spatial pulse length of the 2 wavelengths. Therefore, it takes many compact cell nests separated by a background matrix to reflect the incident ultrasonic energy and yield more echo signals. Our study showed that many fibroblasts in a collagen matrix correlate to a hyperechoic pattern on ultrasound imaging, which corresponded to our hypothesis. In contrast, the accumulation of several uniform tumor cells without a matrix results in hypoechogenicity due to the lack of a significant acoustic impedance difference.

The echotexture of the soft tissue mass as compared with the surrounding tissue was usually classified as showing hyper, iso-, and hypo-echogenicity, with the additional parameter of homogeneity, i.e., homogeneous or heterogeneous. This classification has proven to be unhelpful for differentiation of soft tissue mass,[8,9,12] and even our previous study showed that only large, scallop-shaped tumors with an infiltrative margin had a tendency to be malignant.[12] We think that the usual echotexture grading is probably not adequate to describe histology. In this grading system, there is significant overlapping, which does not show significant differences between echotexture and histology. Therefore, we expanded the grading system to include 7 grades, with each grade further classified as homogeneous or heterogeneous in terms of echo-distribution.

This study shows that if the histology is a single type of cell compactly arranged, such as lymphoma, the ultrasonography will present as marked hypoechogenicity with homogeneous echotexture. If the histology is several tumor cell types compactly arranged, the ultrasonography will present as moderate hypoechogenicity with heterogeneous or homogeneous echotexture. This is possibly because similarly sized tumor cells result in a limited difference in acoustic impedance.

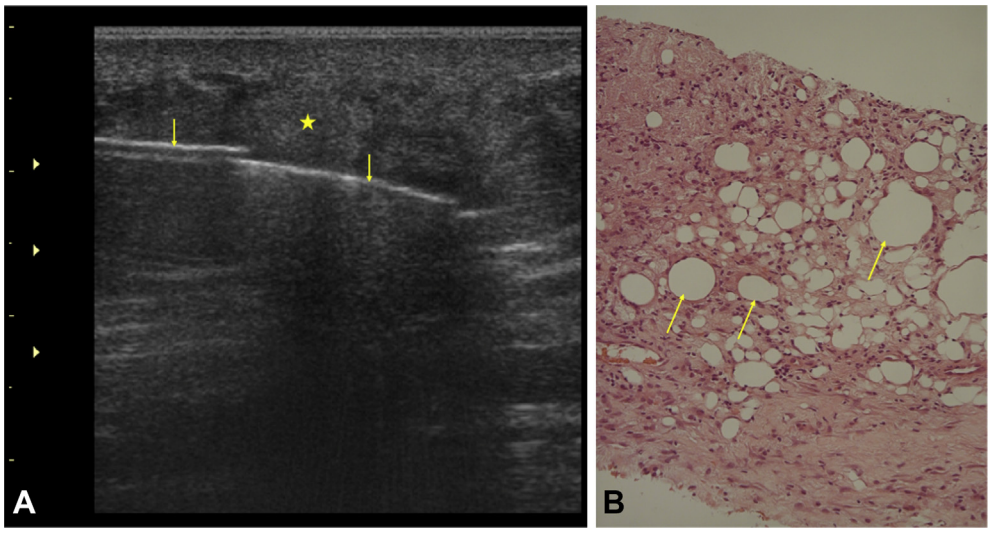

Fig. 2. A 82 y/o male patient complaint of a durable nodule on right buttock region. (A) Ultrasound showed the needle (arrows) within the homogeneous moderate hyperechoic area (asterisk). (B) The histology showed numerous fat cells (arrows) accumulation and separated by connective tissue and inflammatory cells. Turned out to be chronic inflammatory fibrosis.

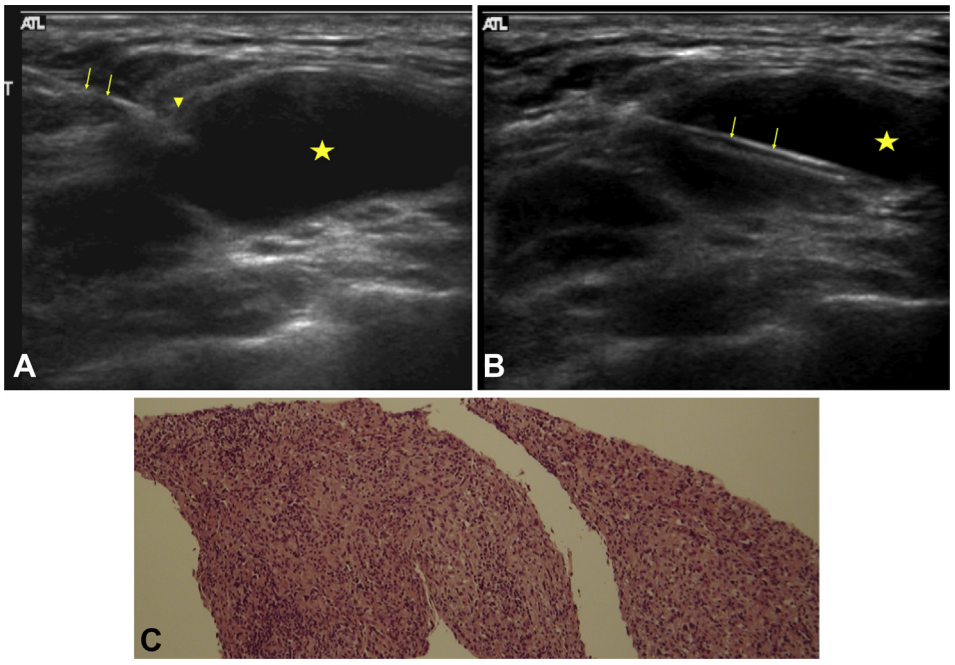

Fig. 3. A 31 y/o female, complaint of palpable nodule in left lower neck. (A) Ultrasound showed initial needle (arrows) touch the capsule (arrowheads) of the tumor (asterisk). (B) Ultrasound showed the needle (arrows) within the homogeneous marked hypoechoic tumor (arrowheads). (C) The histology showed compact of lymphoma cells.

To correlate histology with echotexture, the most important factor to consider is the reflecting interface. Our approach was, therefore, to grade the echotexture from the tissue interface inwards into the tumor and correlate the findings to the histology. In this study, histological classification was assigned according to the difference tissue that resulted in a different interface, such as the cell types or elements and arrangement. The specific cell types, including osteoid matrix, fat cells, and alveolar cells, result in different echogenicity, and their echotextures depend on the arrangement of the tumor cells. Therefore, tumors could be histologically grouped according to cell type and arrangement into those having predominant single cell types arranged compactly, those having several cell types arranged compactly, those with single or multiple tumor cell types arranged loosely, and those with specific cell types arranged compactly or loosely. With this kind of grouping, we could easily correlate the echotexture and echo-distribution of the tumor. Our study showed that the more compact the arrangement of the tumor cells (without a significant amount of matrix), the greater is the homogeneity in echotexture. This

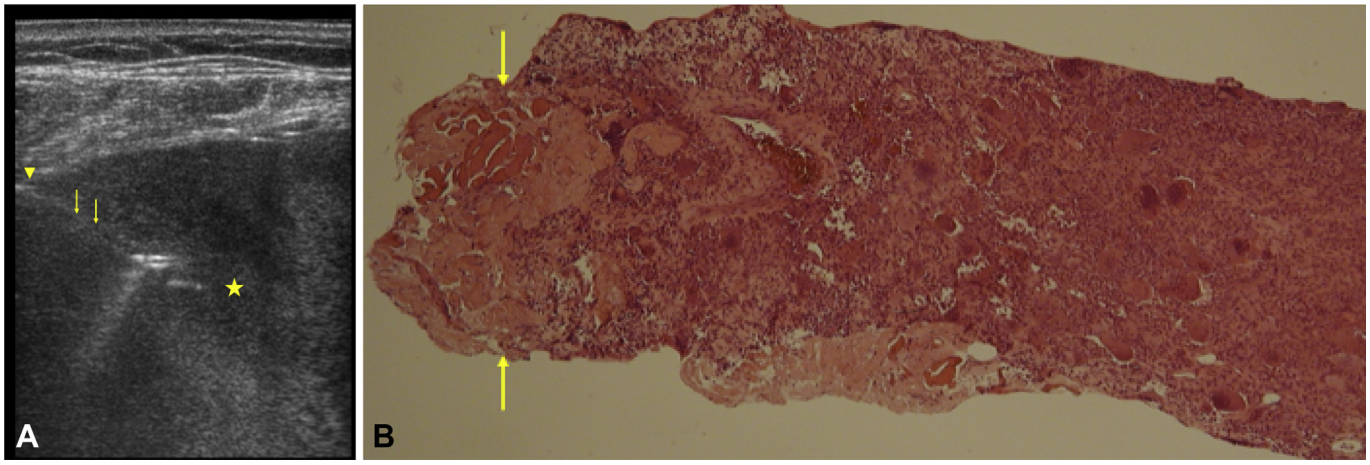

Fig. 4. A 49 y/o female patient complaint of big tumor mass in right upper arm. (A) Ultrasound showed the needle (arrows) through the heterogeneous moderate hyperechoic capsule (arrowhead) and the heterogeneous mild hypoechoic mass (asterisk). (B) The histology showed connective and fibrous tissue (arrows) in the margin of the giant cell tumor.

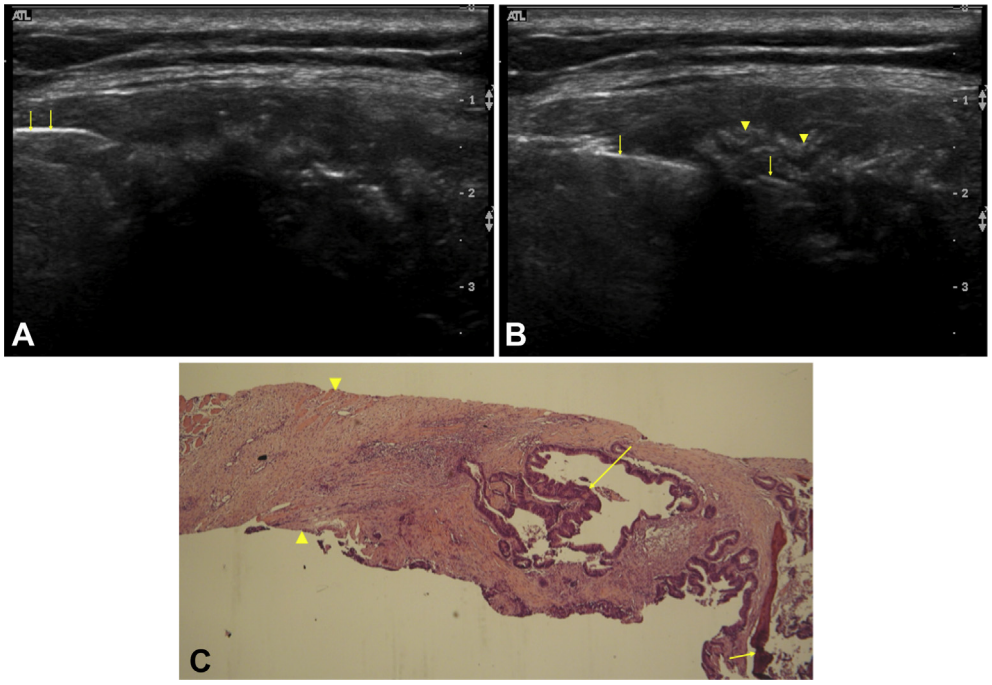

Fig. 5. A 74 y/o female patient complaint of left scapular mass. (A) Ultrasonography showed the initial needle tract (arrows). (B) Ultrasonography showed the needle (arrows) fired through mild echoic muscle, the heterogeneous mild hypoechoic and then the heterogeneous moderate hyperechoic (arrowheads). (C) The histology showed muscle fiber connective tissue (arrowheads), adenocarcinoma (long arrows) and some osteoid tissue (short arrows).

study showed that an ultrasound pattern of marked hypoechogenicity can be correlated to compact arrangement of similar cell types, including the single or several types of tumor cells, compact clustered tumor cells with regular fibroblasts, or several fibroblasts arranged in a curve. These types of different histology could be noted in lymphoma, melanoma metastasis, and chronic inflammation. However, the echo-free cystic structure was avoided to biopsy in this study. Therefore, marked hypoechogenicity is reflected by a solid part in the tumor, rather than a cystic part. When the histology presents as uniform cells, as in the case of lymphoma, there is only small difference in acoustic impedance and the echogenicity. This pattern was mentioned in our previous report.[14]

In our study, homogeneous moderate hypoechogenicity usually correlates to a compact arrangement of clustered tumor cells and rarely, collagen fibers, necrosis, separate fat cells, tiny vessels, some hemorrhage, and fibroblasts distributed in a curve. Therefore, the greater the hypoechogenicity, the more dominant the compact arrangement of tumor cells, and the fewer the number of tumor cell types. Homogeneous minimal hypoechogenicity correlates to compact clustered tumor cells with some chaotically arranged tumor cells,

necrosis, fibroblasts distributed in a curve, alveolar tumor nests with fibroblasts, vessels, and some necrosis. That is, as the number of different cell types increases, the hypoechogenicity decreases. Heterogeneous moderate hypoechogenicity correlates to a compact arrangement of clustered tumor cells with some chaotically arranged tumor cells, necrosis, fibroblasts distributed as a curve, alveolar tumor nests with fibroblasts, and tiny vessels. Therefore, as the number of different cell types increases, the hypoechogenicity becomes more heterogeneous. Heterogeneous minimal hypoechogenicity correlates to a less compact arrangement of mixed tumor cells with collagen fibers, some hemorrhage, vessels, or separate fat cells. The tumor arrangement became less compact, and the amount of surrounding matrix increased, resulting in heterogeneity and less hypoechogenicity. Heterogeneous isoechogenicity was found to correlate to alveolar tumor nests with fibroblasts. The isoechogenicity was possibly due to the alveolar-like space in the tumor cells and some fibroblast cells and collagen fibers. Heterogeneous minimal hyperechogenicity usually correlates to capsules, loose fibroblast, chaotically arranged tumor cells, vessels, clusters of separate fat cells, a mild to moderate number of fibroblasts distributed as a curve, alveolar tumor nests with fibroblasts, chondroid or myxoid tissue, and osteoid tissue. That is, the presence of osteoid tissue, alveolar tumor cells, cluster separated fat cells, and a curved arrangement of fibroblasts will result in increased echogenicity.

In other specific tumor tissues in this study, such as osteoid or calcified tissue, the difference in acoustic impedance increased and resulted in strengthened reflected echoes, causing the ultrasound image to present strong hyperechogenicity. The accumulation of large cells with alveolar appearance, such as alveolar soft part sarcoma, results in iso- to hyperechogenicity, which is possibly due to the increased acoustic impedance of alveolar-type cells. Many fat cells in a fat lobule result in hypoechogenicity, as in the case of subcutaneous fat lobules; however, any matrix, either fluid or cellular, infiltrating into the fat lobules can result in the separation of the fat cells, which will in turn produce a significant difference in the acoustic impedance and result in strong echoes. That is, if fat cells are separated by any soft tissue matrix, the ultrasound image will present homogeneous hyperechogenicity[14,15] and a more compact arrangement of fat cells will result in more homogeneous echogenicity. Our study also showed that if the histology presents as fibroblasts, the echogenicity will depend on the arrangement and grading of compactness of the tumor cells, possibly because of the anisotropy effect. That is, strongly reflected echoes will be produced when the echoes are perpendicular to the cord of clustered fibroblasts, but the echogenicity will be decreased when the echoes are non-perpendicular because of the anisotropy effect. The capsule of tumors is usually formed by a cluster of fibroblasts and collagen fibers; therefore, strong echoes will be produced when sound beams are perpendicular to the capsule. The blood clot within the tumor showed different bleeding times and therefore resulted in different echogenicities, from echo-free in the fluid stage to echogenic in semi-solid or solid stage. Simple fluid accumulation due to the lack of a significant difference in acoustic impedance produced anechoic or hypoechoic results. By studying the histology of soft tissue tumors, we show that their vascular heterogeneity depends on the degree of malignancy. The growth of malignant tumors requires more blood supply, induced by neoangiogenesis including venules and arteries.[16−19] Malignant tumor vessels are histologically characterized by a lack of the muscular layer and by irregular contours. They commonly form a heterogeneous reticular network induced by neovascularization and produce heterogeneity on an ultrasound image. Therefore, we can obtain the viable part of the tumor using ultrasound-guided biopsy.

The major limitation of our study is that ultrasonographic findings are recorded according to consensus by two senior sonologists. Interobserver variability, which may bias our study, was not assessed. Besides, our study findings are based on relative small size of study population which may limit our statistic power. Therefore, the study results of our study should be cautious interpreted. Future studies with larger sample size and using some objective analyze methods to validate our findings are warranted.

In conclusion, echogenicity and echotexture are closely related to histology. For more compact arrangements and fewer cell types, the echotexture is more homogeneous. Echogenicity depends on the difference in tissue acoustic impedance; the smaller the difference, the less is the echogenicity. According to this principle, some types of histology were strongly correlated with the ultrasonographic findings.

Acknowledgments

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