REVIEW ARTICLE

Application of Ultrasonography in Thyroid Cysts

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Thyroid ultrasonography has been used to detect thyroid lesions since the 1960s. In early 1970s, thyroid cyst had been reported to present as thyroid nodules. With over one-third of all isolated thyroid nodules being cystic, over half exhibit cystic degeneration and approximately 17–32% of the cystic thyroid nodules are malignant. The pathogenesis of thyroid cysts is unknown. Possible causes include infarcts and other destructive processes including hemorrhaging in the thyroid follicle, clustering of thyroid follicles followed by cystic degeneration, and benign or malignant tumor necrosis. Cystic fluid analysis for amylase, lactate dehydrogenase and acid phosphatase reveals substantially higher levels than in the serum. Immunoreactive endothelin, vascular epithelial growth factor and β_2-microglobulin were investigated in the cystic fluid of developing and recurrent thyroid nodules. Ultrasound-guided aspiration near the solid part of the thyroid cysts, combined with cytologic study by experienced endocrine cytopathologists, constitutes the best form of preoperative diagnosis of malignant thyroid cysts. Of the malignant cysts, most are papillary thyroid carcinoma. However, medullary cystic carcinoma and anaplastic thyroid carcinoma with cystic changes are also reported. Observation, repeated aspiration, thyroid hormone therapy, percutaneous ethanol injection, ultrasound-guided interstitial laser photocoagulation and surgical treatment are the most common treatment for thyroid cysts. Depending on the definition of response rate and the period of follow-up, the response rate to ethanol injection for thyroid cysts ranges from 72.1% to 93.9%. In conclusion, the pathogenesis of the thyroid cysts requires further investigation. Recurrent thyroid cysts larger than 3 cm may require surgical treatment.

KEY WORDS — fine needle aspiration cytology, sclerotherapy, thyroglobulin, ultrasonography, vascular epithelial growth factor

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Introduction

Thyroid cysts are common in humans as well as in animals [1]. Hemorrhagic thyroid cysts were recorded in 1950 in MEDLINE [2]. Otherwise, thyroid cysts remain a loosely defined term for thyroid disease. Before the widespread application of ultrasonography, a cyst was defined as any fluid-filled

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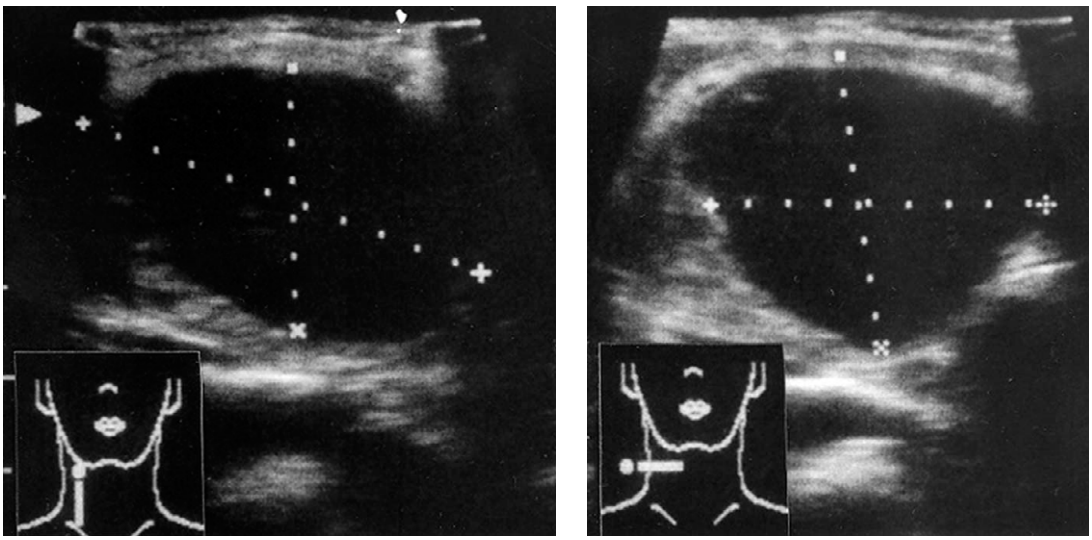

Fig. 1. *Ultrasonography of a simple cyst in the right thyroid of a 45-year-old male presenting with smooth wall. (Real-time mode with a 10 MHz transducer)*

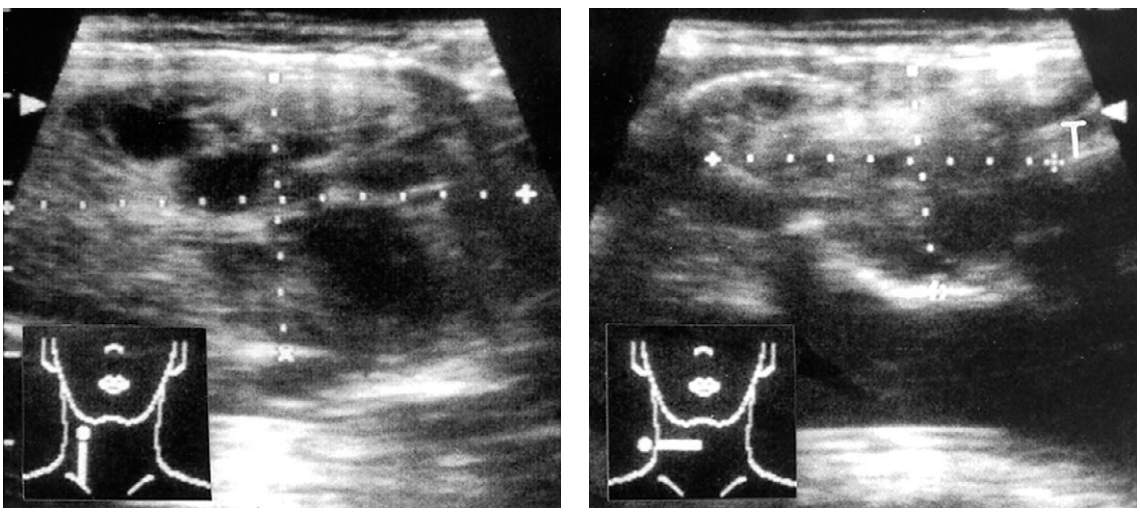

Fig. 2. *Thyroid ultrasonography of 32 female patients presenting with right thyroid nodule and multiple cystic degeneration.*

cavity exceeding 1 cm in diameter or aspirated cystic fluid over 2 mL [3,4]. Because most thyroid cysts are benign lesions, they do not normally receive surgical treatment. The incidence of thyroid cancer in thyroid cysts and cystic degeneration of thyroid cysts is difficult to determine. Depending on how a thyroid cyst is defined, over one-third of all isolated thyroid nodules are cysts [5]. Fine needle aspiration cytology (FNAC) is conventionally used to distinguish benign from malignant thyroid nodules. The diagnostic accuracy of thyroid ultrasonography with FNAC of solid thyroid nodules is widely recognized by clinicians. In cystic changes of the thyroid masses, the accuracy is less clear [6,7].

Clinical Features

Most thyroid cysts are benign thyroid lesions. However, a few of the thyroid cysts present as simple cysts (Fig. 1). Most thyroid cysts present with nodular goiter with cystic change or thyroid cysts with septum (Figs. 2 and 3). Anatomic terms,

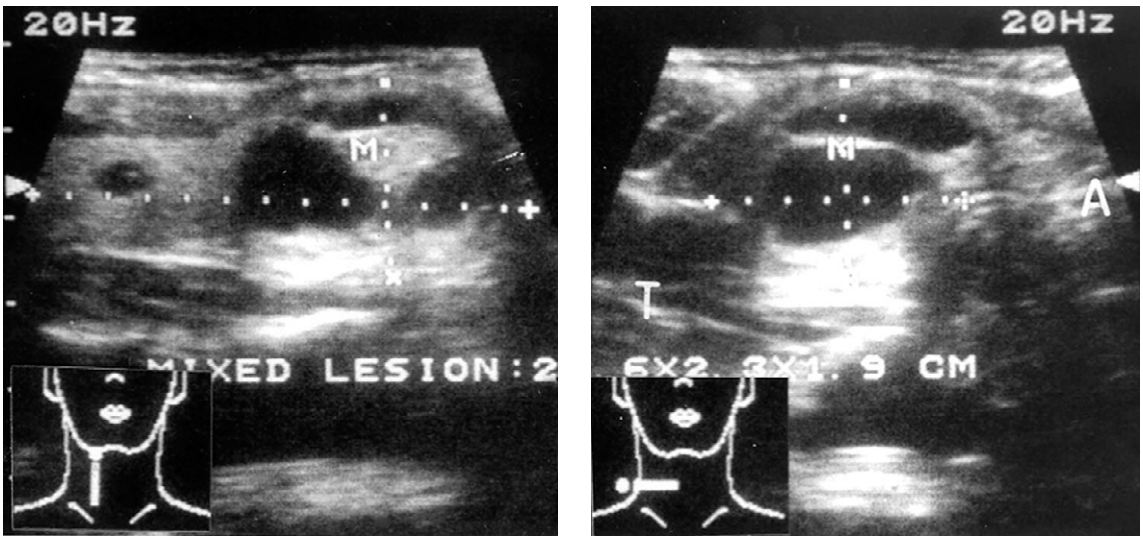

Fig. 3. *Right thyroid cyst in 42 female patients with septum in the cyst.*

such as mixed lesion or complex lesion, are used sometimes in thyroid ultrasonographic examination. Before the widespread use of thyroid ultrasonography, differentiating simple cysts from the other complex lesions was difficult. Improvements in ultrasonographic technology and imaging resolution currently allow the identification of cysts less than 5 mm in size. A recent retrospective study reviewed ultrasonographic data of 6,219 patients with thyroid nodules treated in a single medical center [8]. The data revealed 1,983 cystic changes and 4,236 solid masses. Following FNAC examination, 506 (11.9%) patients with solid masses underwent surgical treatment, in comparison with 143 with cystic changes in thyroid masses (7.2%). Of the 649 nodules treated surgically, 29.8% (151/506) and 9.1% (13/143) were malignant in the solid and cystic change groups, respectively. Overall, after surgical treatment, 0.65% of cystic changes in thyroid lesions were diagnosed as thyroid cancer. Diagnostic accuracy of FNAC in cystic changes of the thyroid masses after ultrasonographic examination was comparable to that for solid thyroid nodules. Determining the precise incidence of malignancy in thyroid cystic changes is difficult, because prospective studies of surgical treatment for all thyroid cystic changes are not possible. A specific sonographic sign, with multiple punctate echogenic foci suggesting calcification in solid excrescences protruding into the cysts, has been identified as specific to cystic change of papillary thyroid carcinoma [9]. Diagnostic accuracy of FNAC in cystic change of thyroid malignancies is usually lower than that in solid masses, with sensitivity and specificity of 88% and 52%, respectively, for cystic change in papillary thyroid carcinoma reported in one study [10]. Diagnostic accuracy depends on the case and diagnostic procedure employed.

Surgery has previously been recommended for patients with thyroid cystic changes exceeding 3 cm, those with persistent growth or if repeated aspiration does not yield adequate cells for interpretation of FNAC [11]. To improve diagnostic accuracy, ultrasound-guided FNAC and cytologic criteria for cystic change in papillary carcinoma have been used [12–14]. Atypical cells or indeterminate cells revealed by FNAC, indicating thyroid cystic changes later shown to be malignant, may exhibit cohesive flat sheets, distinct cell borders, nuclear enlargement, nuclear grooves, dense granular cytoplasma, small distinct nucleoli, fine chromatin, and elongated or spindled cytomorphology [15]. No specific features of cytomorphology are characteristic of cystic change of thyroid cancer unless aspirated from the solid portion of mixed thyroid nodules. As in previous investigations, the incidence of pre-operatively diagnosed carcinoma was low in thyroid cystic changes after FNAC [16]. Inconclusive results of FNAC for

thyroid cystic changes are common because of the difficulty in obtaining adequate cells [7,17]. Although repeat aspiration or centrifugation of the aspirates may yield improved results [11], accurate diagnosis of larger cystic changes (e.g. >3 cm) remains problematic.

Pathologic and Biochemical Characteristics of Thyroid Cysts

The content and composition of thyroid cysts may vary. Contents may include thick colloids, a gelatinous substance, hemorrhagic brownish fluid, chocolate-colored fluid or clear yellowish fluid. Cystic thyroid disorders may result from clear fluid cysts, thick colloid cysts, cystic echinococcosis [18], hydatic cysts [19], intrathyroidal thyroglossal ducts cyst [20], lymphoepithelial cysts [21], epithelial cysts, epidermoid cysts [22,23], thyroid abscess [24] or various thyroid cancers [25–27]. Histopathologic findings for thyroid cysts may reveal simple cysts, colloid degeneration, colloid adenoma, follicular adenoma, malignancy or thyroiditis. Although the nature of cystic transformation in thyroid cancer is unknown, different histopathologic patterns of thyroid carcinoma have been documented. Diagnostic pitfalls may be present in both papillary thyroid carcinoma with cystic change in primary tumor site and in metastatic lymph nodes and the follicular neoplasm [28]. Figure 4 presents the histopathologic features of different benign and malignant cysts. Most malignant thyroid cysts are papillary thyroid carcinoma (Fig. 4C). Histologically, thyroid

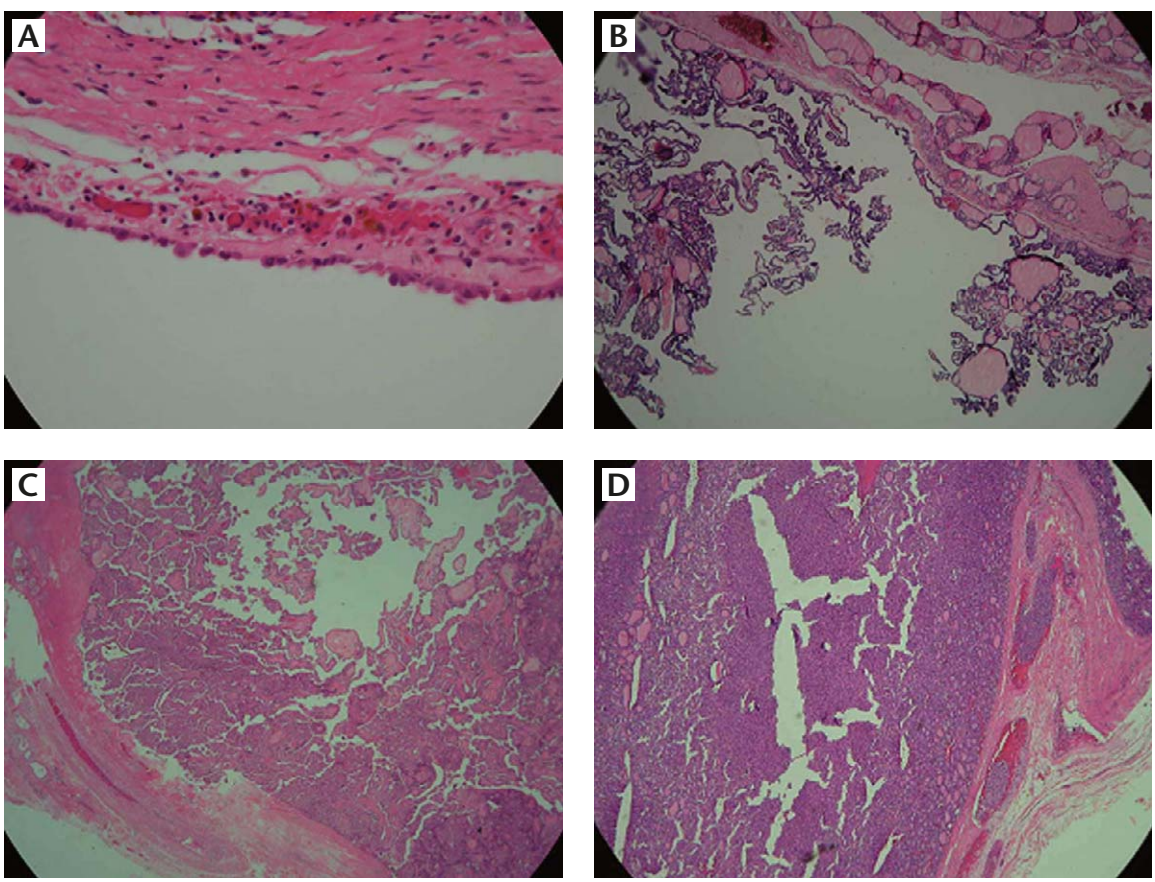

Fig. 4. *Histologic examination of a thyroid cyst may show (A) simple thyroid cyst lined by a single layer of follicular cells, (B) thyroid cyst with papillary hyperplasia, (C) papillary thyroid carcinoma with cystic degeneration, or (D) follicular thyroid carcinoma with cystic degeneration. Adapted from Lin et al [8].*

cysts may be the result of cystic degeneration of nodular goiter, follicular adenoma, papillary carcinoma or follicular carcinoma.

Surgically proven benign and malignant cystic fluids contain the thyroid hormones thyroxine and triiodothyronine, thyroglobulin, and thyroxine-binding globulin. None of these assays could distinguish benignity from malignancy. Biochemical analysis of amylase, lactate dehydrogenase and acid phosphatase showed much higher levels in the cystic fluids than in the serum. The elevated activity of these enzymes was considered to be thyroidal in origin [29]. Increased aspartate aminotransferase, lactate dehydrogenase activity, and high concentration of total protein, uric acid, iron and total bilirubin indicated red blood cell sources with recent and previous hemorrhages. Concentrations of glucose, cholesterol and triglyceride in the cyst fluid were within the normal serum range [29]. The gross appearance of the fluid, together with the presence of biochemical substances, suggested a hemorrhagic origin for most cysts. Other possibilities were autolysis or necrosis of thyroid tissue and inflammation.

Pathogenesis

In earlier studies, the structure and motility of primary cilia in the follicular epithelium of the human thyroid has been demonstrated in normal, benign and malignant thyroid tissues [30–32]. Histologic observation has disclosed two epithelial cells: columnar epithelium with mucous content or with cilia, and squamous epithelium with or without keratinization [33]. The presence of cilia may be used as a marker for differentiating thyroid follicular cells. Immunohistochemical profiles of epithelial cells are used to characterize cyst origins in organs such as liver or spleen [34–37].

The cyst may emerge from infarcts or other destructive processes such as hemorrhage in preexisting follicles or cavities [32]. Three-dimensional comparison of the colloid goiter or preexisting adenoma had revealed that large vessels are mainly located at the nodule periphery while the parenchyma contains only rare thin vessels [38]. Infarction may occur after continuous growth of the thyroid nodules. The mechanism whereby expanding thyroid follicles become enlarged over 100 times (from 50 μm to 0.5 cm for instance) as a thyroid cyst is unknown. Any insult causing subepithelial inflammatory process or hemorrhage of the thyroid follicle may elevate the pressure of perifollicular space. The increased pressure may affect microcirculation in the subepithelial area.

Thyroid cysts with multiple septa are not unusual (Fig. 3). Following aspiration in the deepest portion of the cyst, more fluid appears upon withdrawal of the needle to the superficial portion. The origin of these "cysts within a cyst" is difficult to determine by tumor necrosis or septa growth from the wall of the cyst. A possible mechanism is clustering of the thyroid follicles followed by cystic degeneration. In both benign and malignant thyroid tumors, the balance between cell proliferation and cell death is important to maintain tissue homeostasis. Apoptosis and cell necrosis are major processes in thyroid epithelial cell death. In contrast to normal cells, the majority of goiter cells do not respond to TRAIL- or Fas-mediated apoptosis by cytokine pretreatment [39]. Necrosis is due to a relatively insufficient blood supply which cannot sustain the growth of replicating neoplasia [40,41]. Vessel distribution in benign and malignant thyroid lesions has been studied with histologic stereomicroscopic three-dimensional reconstruction [38]. Poorly differentiated follicular thyroid carcinoma and medullary carcinoma contain large intratumoral vessels surrounding avascular areas corresponding to solid neoplastic cellular sheets with necrosis. Papillary thyroid carcinomas are more vascularized and contain numerous vascular anastomoses. Further information is needed concerning cytokines, growth factors as vascular endothelial growth factor (VEGF), immunoreactive endothelin [42], β_2-microglobulin [43] or any tumor marker in the cystic fluid which could distinguish benign from malignant cysts [44]. Differences in pathogenesis between benign and malignant thyroid cysts need further investigation.

Ultrasound Diagnosis and Differential Diagnosis

Ultrasonographic and pathologic correlations reported from Japan revealed that 17% of thyroid cysts were malignant [45]. Of the various sonographic findings of cystic thyroid masses, oval cystic lesions, with a polyp or dome-like solid component projecting into the lumen, were all identified as adenomatous goiter (Fig. 5). Uneven cystic structures, with finger-like pedunculated mass of more than 2 cm thrust into and/or out of lumen, were all diagnosed as papillary carcinoma. Small oval cysts (≤ 1 cm) with strong echo were all confirmed as colloid goiter. Size of the thyroid cyst should not be regarded as differentiating benignity from malignancy. Timing of the ultrasonographic examination during tumor growth is important. When thyroid ultrasonography is used after detection of thyroid nodule by physical examination, most tumors prove to be larger than 1 cm. Thyroid cysts may demonstrate coexistence with thyroid microcarcinoma in the thyroid cystic wall. These thyroid papillary microcarcinomas in the thyroid cysts were mostly incidental findings in the final histopathology after surgery.

Differential diagnosis should be considered for thyroglossal duct cyst and parathyroid cyst. The thyroglossal duct forms during descent of the thyroid from the foramen cecum at the base of the tongue and normally disappears during the sixth or seventh gestational week. One percent of thyroid cancer evolves from the thyroglossal duct cyst, and 1.5% of thyroglossal duct cysts have been diagnosed with well-differentiated thyroid carcinoma [46,47]. This carcinoma has often been diagnosed incidentally after surgical excision. Like thyroid cysts, benign thyroglossal duct cyst presents with an anechoic pattern at ultrasonographies, whereas cysts containing carcinoma and adenoma show a mural nodule [48]. In a previous study, FNAC proved to be the best and cheapest method of diagnosis for thyroid cancer in thyroglossal duct cyst [49]. Results for surgical procedures and follow-up of thyroglossal duct with cancer are usually comparable for well-differentiated thyroid cancer. The Sistrunk operation is adequate for most patients with incidentally diagnosed thyroglossal duct cysts, in the presence of clinically and radiologically normal thyroid gland. The 5- and 10-year Kaplan–Meier survival rates were 100 and 95.6%, respectively [50].

Parathyroid cystic lesions account for an estimated 1–5% of neck cysts [51]. They may present as neck swellings that may be mistaken both clinically and cytologically as thyroid nodules [52]. Pathologically, parathyroid lesions may include simple cysts, hyperplasia, adenoma or carcinoma [51,53, 54]. In contrast to thyroid cysts, most parathyroid cysts were aspirated as clear, colorless or watery fluid. Extremely high levels of calcium and C-terminal mid-molecule parathyroid hormone assay could be detected. Although intracystic parathormone measurement is important for diagnosis, only two cases

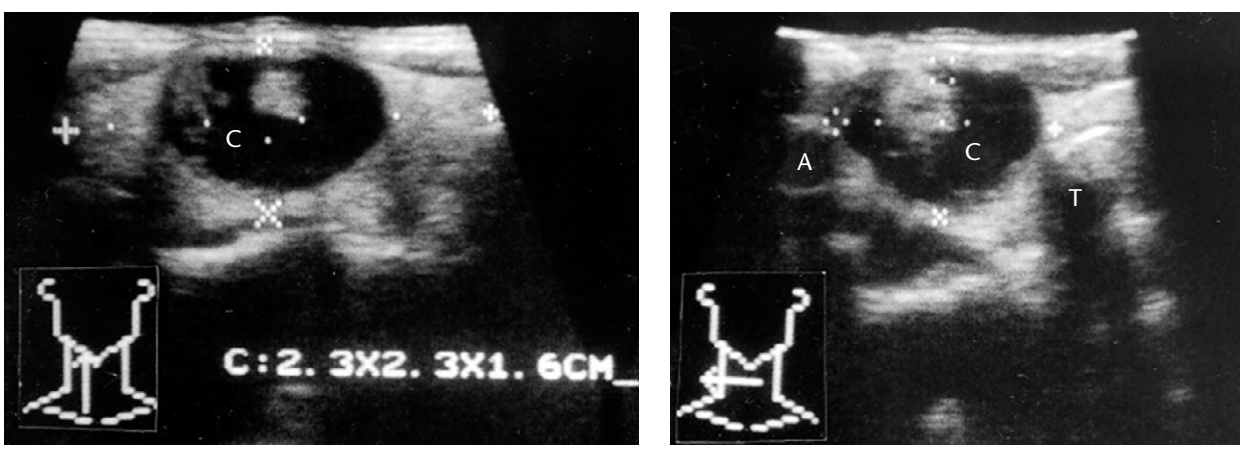

Fig. 5. *Polyp or dome-like solid component projecting into the lumen of the right thyroid cyst. A = artery; C = cyst; T = trachea.*

out of the 10 parathyroid cysts were measured in one study [55]. Differential diagnosis of thyroid cysts with parathyroid, preoperatively, is important. Most parathyroid enlargements presenting in ultrasonographies are hypoechoic to anechoic lesions. When ultrasonography reveals cystic lesions near the posterior thyroid capsule, parathyroid cyst or enlargement should be listed as the differential diagnosis.

Therapy for Thyroid Cyst

Application of thyroid ultrasonography changes the therapeutic modality for thyroid cyst. Most thyroid cysts were previously diagnosed and treated with surgery. In addition to ultrasonography, observation, repeat aspiration [56–58], thyroid hormone therapy [56,59] and sclerotherapy [4,60–62], laser photocoagulation [63] and surgical treatment [7] are the main methods for treating thyroid cysts. Because of the benign clinical course of most thyroid cysts, few investigations have reported prospective long-term follow-up for benign thyroid cyst. One recent study of 1-month to 5-year follow-up examinations revealed that nodules with greater cystic content were less likely to grow, compared with solid nodules [64]. The estimated proportion of nodules with a 15% or greater increase in volume after 5 years was 89%. Prior to determining non-surgical treatment for thyroid cysts, definite diagnosis as benign lesion is crucial.

A study of instillation of intracystic tetracycline hydrochloride treatment was conducted in nine patients following repeat cyst aspiration [65]. After a mean of 40 months of follow-up, all except two of the cysts were completely resolved. Follow-up studies revealed a 43–95% response rate for the tetracycline treatment [66–68]. A randomized double-blind study was performed in 66 consecutive recurrent and benign patients. A recent study compared ethanol instillation with isotonic saline and subsequent complete emptying for treating recurrent thyroid cysts [4]. An 18–64% rate of cure was observed in both groups. Efficacy of percutaneous ethanol injection for treating thyroid cysts versus solid thyroid nodules has proven superior in cysts. Volume reductions of 65–38.3% ($p < 0.01$) were observed in both groups [60]. In contrast to tetracycline sclerotherapy, hydrochloric acid (pH 1.0) has been used to treat thyroid cysts [61]. Hydrochloric acid demonstrates no advantage over ethanol injection. A prospective, large series study of 98 symptomatic thyroid cystic nodules explored the long-term efficacy of percutaneous ethanol injection over a follow-up of 9 years. In 92 of 98 patients with more than 50% nodule shrinkage, only six of the 92 respondents relapsed. In summary, ethanol injection is an effective, inexpensive procedure with high patient compliance and long-term effects in treating cysts larger than 40 mL [61]. Depending on the definition of response rate and period of follow-up, the response rates of ethanol injection for thyroid cyst range from 72.1% to 93.9% [4,62,69,70].

Thyroid cysts are often surgically removed to minimize malignancy and recurrence after repeat aspiration [71]. Approximately 55% of cystic papillary thyroid carcinoma revealed false-negative results in a retrospective study [25]. Recurrence after two aspirations of cystic fluid, together with suspected malignancy in aspiration cytology or in cysts larger than 3 cm, are considered indications for surgical removal of the cysts [63,72]. Figure 6 lists recommended diagnosis and therapy for thyroid cysts or

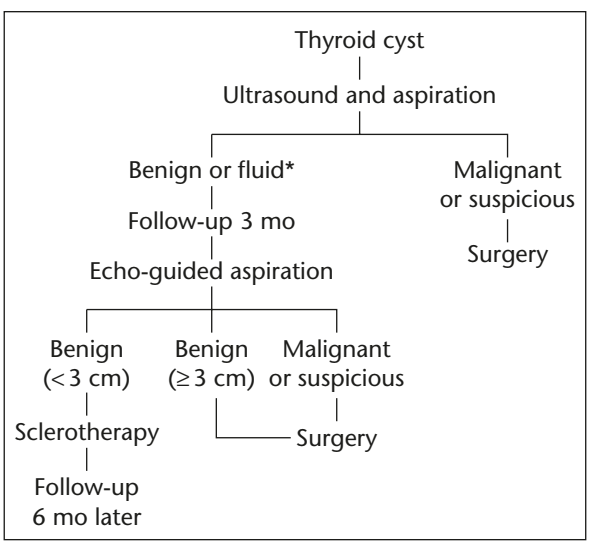

Fig. 6. *Flowchart for diagnosis and recommended therapy for thyroid cysts. *Aspiration from solid portion if possible.*

cystic degeneration of thyroid nodules. Percutaneous ethanol injection is the recommended treatment for cystic thyroid lesions by the American Association of Clinical Endocrinologists [73]. Sclerotherapy is not the routine therapeutic modality in most Taiwan hospitals. Furthermore, this more "invasive therapy" carries risks of complications; most of these cases receive follow-up ultrasonography and repeat FNAC for 6–12 months. Enlarged cysts after repeated aspirations are an indication for surgical treatment (Fig. 7).

Prospective studies of surgical treatment for all thyroid cysts are not possible. Definitions of thyroid cysts vary considerably. Although other histologic

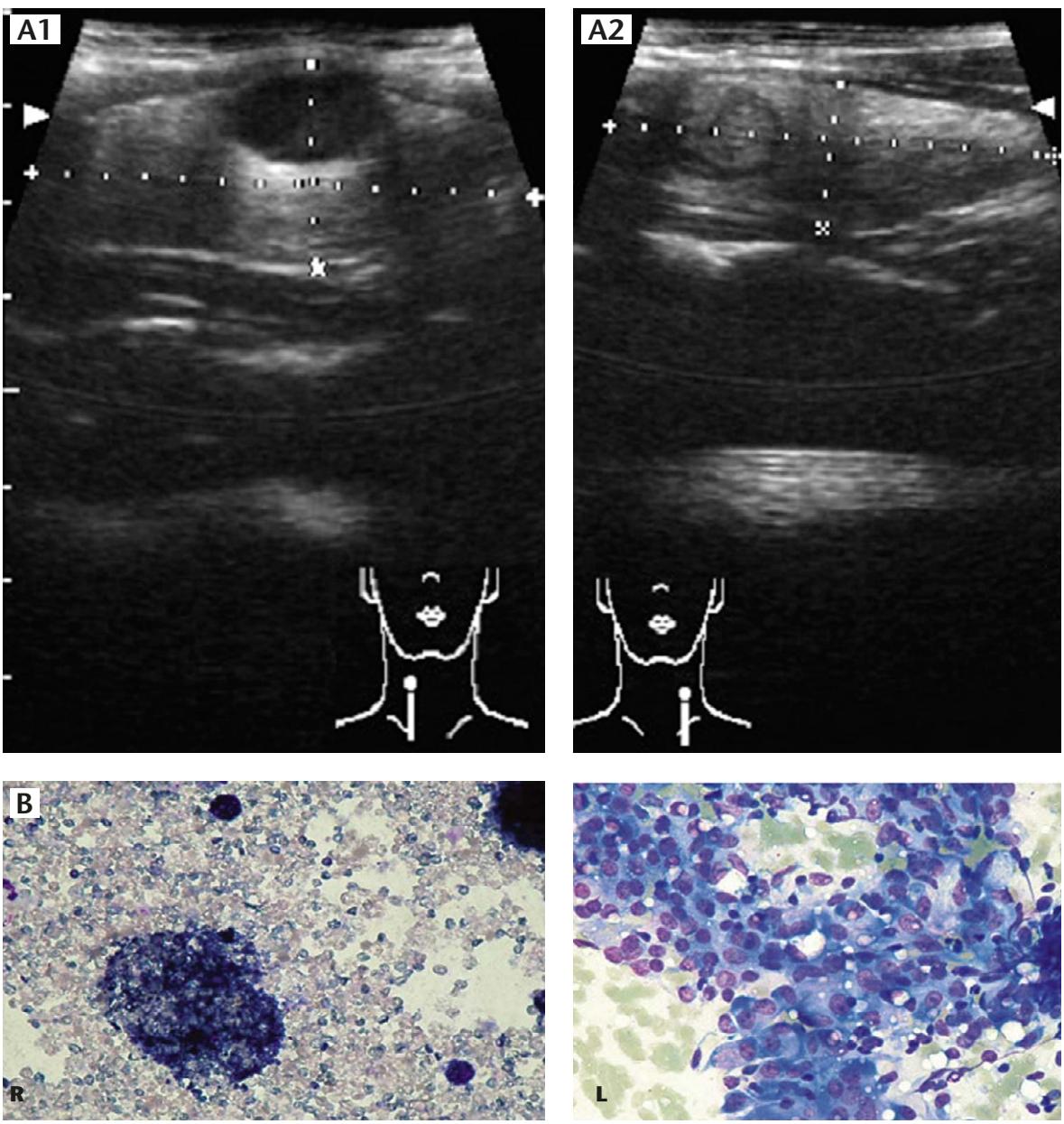

Fig. 7. *A 39-year-old female presented with bilateral thyroid nodules. (A) Ultrasonography of thyroid nodules. Right thyroid (A1) with cyst and left thyroid (A2) with isoechoic solid mass with complete "halo" sign. (B) Liu's stain of fine needle aspiration cytology from bilateral thyroid nodules. Surgically proved this case with right nodular hyperplasia with cystic degeneration and left follicular variant of papillary thyroid carcinoma.*

types of thyroid cancer with cyst have been documented [74,75], papillary thyroid carcinoma has proven to be the most common histologic type. Further study is needed to clarify the actual incidence of cysts in different thyroid cancers. Pathophysiology of cystic changes in different thyroid cancers also requires further investigation. Diagnostic accuracy of FNAC in these cystic thyroid malignancies is usually lower than in solid masses. Sensitivity and specificity of 88% and 52%, respectively, to cystic papillary thyroid carcinoma was observed in one study [10]. Detailed classification of thyroid cysts in seven categories has been reported [76]. Eighty percent of malignancies involve larger cysts with projections exceeding 1 cm and unevenly mixed cystic and solid components. A specific sonographic finding of multiple punctate echogenic foci, suggesting calcification in solid excrescences protruding into the cyst, has been specifically identified as cystic papillary thyroid carcinoma [9]. Cystic degeneration of the metastatic lymph node of the papillary thyroid carcinoma is commonly observed [28,77,78], although the primary tumor may appear as a solid mass in the thyroid. Comparison of patient demographics, including age, gender, tumor size, and prognosis of the cystic and solid thyroid cancers demonstrate no statistical difference [9].

Conclusion

Pathogenesis of thyroid cysts in benign and malignant nodules requires further investigation. The VEGF level, galectin-3 or comparison of 53P, telomerase activity in aspirate from the cysts may serve as differentiation markers between benign and malignant cysts. In conclusion, more data are needed to clarify the role of growth factors or oncogenes in the growth and malignant transformation of these lesions. Sclerosing therapy is effective in compressive and cosmetic symptoms for most benign cysts. However, ultrasonographic guided FNAC with careful cytologic interpretation is crucial to avert misdiagnosing malignant cysts.

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