Management of Atypia of Undetermined Significant Thyroid Nodule

Ika Dewi Mayangsari*and Ferucha Moulanda

Division of Oncology, Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia
**Corresponding author. Email: idmayang@yahoo.com*

ABSTRACT
Thyroid nodules are one of frequent clinical problem with prevalence of 5% palpable nodules. Results of atypia of undetermined significance (AUS) can be found with risk of 5-15% malignancy rates. Management of AUS is still challenging and complex including observation until surgical approach. We present two cases of nodule thyroid. The 1st case of 44-year-old female with nodule of left thyroid lobe for 1 year. Ultrasonography (USG) examination showed TIRADS 4 at left lobe yet the Fine needle aspiration (FNA) resulted as AUS. The 2nd case was 44-year-old male with nodule at left thyroid lobe for 3 years. USG showed TIRADS 5 of left lobe and TIRADS 4 of right lobe meanwhile FNA resulted as AUS. Left hemithyroidectomy was performed for the 1st patient and histopathology examinations showed as struma adenomatous with focus of thyroid papillary carcinoma with follicular variant. Completion thyroidectomy then performed 2 months after the first procedure. Observation was chosen for the 2nd case. Patient has been asymptomatic with close thyroid function and USG follow up. Hemithyroidectomy was performed 6 months afterwards since the mass getting bigger, and histopathology showed papillary carcinoma thus proceed with total thyroidectomy. Management of AUS is still debatable. It can present as heterogeneous lesions with different sub classifications according to cytomorphologic and molecular findings. Considerations of clinical risk stratification, USG findings and FNAB should be combined altogether for the best management and treatment outcome.

Keywords: *AUS, hemithyroidectomy, management, thyroid nodule.*

1. INTRODUCTION

The prevalence of thyroid nodules found by palpation was 4.2% and its quite common in population. Prevalence in female is 4 times higher than male. Malignant nodules are found in 5–15% cases. This prevalence was reported increased by age. Various imaging techniques such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) have been developed for diagnosis of thyroid nodules. Ultrasonography (US) reported can detect the nodule as high as 67%.[1-3]

Fine needle aspiration (FNA) is the most valuable, cost effective and accurate method in the evaluation of thyroid nodule. The sensitivity was reported 65-98% and specificity 72-100%. Cytology examination was reported using Bethesda system. One of the challenging criteria is type III Bethesda known as AUS/FLUS. It can occur in 3-18% of thyroid nodules. Several recommendations are made for the management and follow up of these criteria. For malignancy risk assessment suspected in clinical and US features suggested to proceed with repeat FNA and molecular testing. Surveillance or diagnostic surgical procedure can be performed if repeat FNA and molecular testing are not available or both are inconclusive. Surgical management in cytologically indeterminate nodules (AUS/FLUS, FN/ SFN, SUSP) can be either hemithyroidectomy, near total or total thyroidectomy. Procedure chosen based on clinical risk factors (large nodule >4 cm, family history and history of radiation), findings on USG, FNA, and molecular testing [1,4].

Diverse management options for Bethesda class III nodule have been suggested, including clinical observation, follow- up ultrasound, repeat FNA, molecular testing or surgery. Patient's wishes or experiences of the surgeons can be considered in determining therapeutic options [5]. Aim of this paper is to report 2 cases of thyroid nodule in different gender with FNA resulted as AUS that treated in our center.

2. CASE REPORT

We present two cases of nodule thyroid. The 1st case of 44-year-old female with nodule of left thyroid lobe for 1 year. Patient has history of non-Hodgkin malignant lymphoma and has finished 7 cycles of chemotherapy then scheduled for radiation therapy. There were no history of palpitation and extreme loss of body weight. USG examination and USG-guided FNA were performed. AUS was found form FNA meanwhile USG thyroid showed 2.7x3.3 cm in size of left lobe and normal right thyroid accordance with TIRADS 4 of left lobe. CT Scan of neck area showed solid mass at left thyroid lobe sized 3.8 cm. According to the clinical risk stratification based on GAMES (gender, age, metastasis, extrathyroidal extension and size) patient has lower risk, however hemithyroidectomy was performed due to the radiation schedule and high TIRADS grade (Fig.1). Histopathology examination showed adenomatous struma with papillary hyperplasia and thyroid papillary microcarcinoma focus. Completion thyroidectomy was performed 2 months afterwards. Histopathology examination showed struma with microcarcinoma papillary and negative metastasis in central lymph node.

Figure 1. Lump at left thyroid, CT scan and surgery procedure (left hemithyroidectomy)

The 2nd case was 44-year-old male with nodule at left thyroid lobe for 3 years. It was painless, and there were no history of palpitation or extreme loss of body weight. USG showed TIRADS 5 of left lobe with size 4.3x2.6x5.7 cm and TIRADS 4 of right lobe sized 0.9x0.6x1.1 cm. FNA resulted as AUS and thyroid function (TSHs, FT3 and FT4) was normal. Thyroid scan resulted as inhomogenitas thyroid bilateral with low total thyroid intake. According to GAMES criteria, patient was stratified as low-moderate criteria then proceed with 6 months surveillance. Repeat USG thyroid showed left thyroid lobe sized 3x4.5x5.4 cm with TIRADS 5 and multiple lesion (cyst and solid) at right lobe with biggest size 0.5x0.6x0.9 cm with TIRADS 2 for cystic lesion and TIRADS 4 for solid nodule. CT Scan showed solid mass at left thyroid lobe sized 4.3x4.4x5.8 cm (Fig.2). Left hemithyroidectomy then performed. Frozen section of left thyroid lobe, central lymph node and biopsy of right lobe are positive for malignancy. Completion thyroidectomy directly performed continued with left lateral neck dissection (Fig.3). Patient was currently waiting for definitive histopatholgy result and scheduled for consultation to endocrinologist and ablation therapy.

Figure 2. Lump at left thyroid and CT Scan thyroid

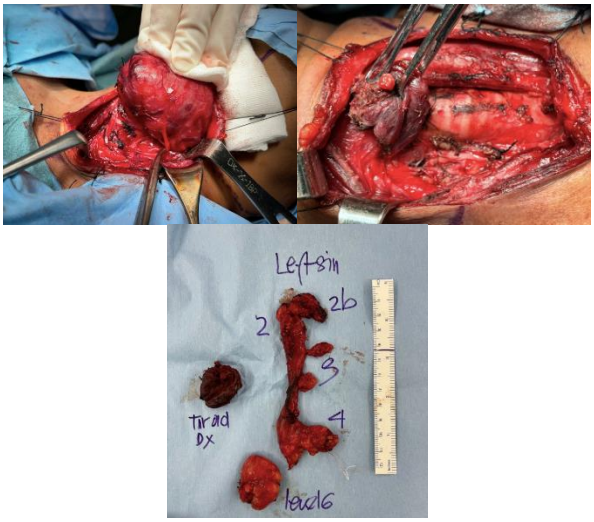

Figure 3. Surgery procedure (Total thyroidectomy and lateral left neck dissection)

3. DISCUSSION

According to the Bethesda system for reporting thyroid cytology (TBSRT), AUS terminology will be used when the aspirates of thyroid FNA is adequate but there are not enough cytologic findings to confirm it as "benign follicular nodule" or "follicular neoplasm" or "malignant," then the phrase of "atypical cell of undetermined significance/follicular lesion of undetermined significance". Risk of malignancy is reported happen in 5-15% of AUS cases. Study by Geramizadeh et al[4] reported malignancy in 5-48% and mostly reported as papillary thyroid cancer (PTC). The

risk of malignancy related to the nuclear atypia rather than architectural atypia. Previous study showed that the presence of 2 nuclear features will increase the risk of malignancy up to 30-33% and will reach up to 100% when 4 nuclear features appeared [6,7]

The AUS category comprises a heterogeneous group of findings, and the risk of malignancy associated with the nature of the observed atypia [8]. Most guidelines have recommended close follow-up for the AUS and repeating USG-guided FNA [7]. It recommended to use approximately in 7-10% of all thyroid FNAs. However, some studies reported overuse diagnosis tendency of AUS/FLUS and the reported malignancy risk varies from the proposed rate by 14% to 38% [9,10]. FNA is the initial and accurate assessment for diagnosing a thyroid nodule. Sensitivity and specificity of FNA procedures reported around 61.8%–98.4% and 71.4%–100% respectively but the accuracy is lower in AUS type. Some researcher found that malignant cases is found in 6%-48% AUS. Other factors are useful for AUS risk stratification such as sex, age, and nodule size. One meta-analysis reported that male is a risk factor for malignancy in patients with indeterminate thyroid nodules. One study showed that the increased nodule size (≥2 cm) and younger age (<65 years) were associated with triage to surgery. The 2015 ATA guidelines rely on the concept of risk stratification and generally recommended more conservative management to prevent overdiagnosis and overtreatment [10-13]. Repeat FNA is recommended at appropriate intervals. Recurrent diagnosis of AUS can occur in 19-31% cases in repeat FNA, and in some study 43% of repeat FNA cases was proceed with surgery with malignancy rate 27% [4,6,11]. Ogmen et al [11] reported 5.4% AUS cases in their study and 29.3% of those cases were histopathologically malignant. Study by Yassa et al[14] showed that repeat FNA can lead to 80% definitive diagnosis, however risk of inconclusive readings, nondiagnostic and AUS can occur in 20% - 49.1% of nodules with previous AUS FNA readings [6,12]

Core needle biopsy (CNB) was recently introduced as a safe and effective procedure in diagnosing indeterminate thyroid nodules to prevent overtreatment. Some studies reported that CNB can classify as much as 98% of indeterminate thyroid nodules. Yim et al [16] reported that CNB has diagnosis sensitivity of 91% (95% CI, 81–96%) and specificity of 99% (95% CI, 98–100%) [16]. Complications related to CNB are massive hematoma, pseudoaneurysm, voice problems. No significant difference compared to complication of FNA in terms of pain, tolerability and complications [16]. Choi et al [7] reported 65% risk of malignancy found with CNB with significantly high occurrence of PTC [7].

USG remain the important tools in initial evaluation because it can help to confirm size, location and evaluate the composition, echogenicity, margin, presence of calcification, shape and vascularity of the nodules and the adjacent structures.[10] Higher likelihood of malignancy characterized by a shape that is taller than wide, hypoechogenicity, irregular margins, presence of microcalcifications, abnormalities of vasculature, increasing size and absent halo [2] Risk of malignancy reported as high of 40.4% if one of the features is present, increase to 66.7% if two are present and decrease to 5.3% if no malignant features are present [13].

Gao et al [14] reported that 50% of AUS cases become benign. Their center recommended a triage procedure of repeat FNA, US and *BRAFV600E* gene mutation. The most common triage in AUS is the molecular analysis [2,4]. The strategies of molecular testing are mutational analysis and gene expression analysis. Mutational analysis comprised of BRAF, NRAS, HRAS and KRAS point mutations, rearrangements of RET/PTC1 and 3, and PAX8/PPARγ reported with high specificity (86–100%), poor sensitivity (44-100%) and positive predictive value (PPV) of 84–100%. This analysis is used as a **rule in test.** Gene expression classifier (GEC) evaluates for the presence of a benign gene expression profile. This analysis has a sensitivity of 92%, specificity of 48-53%, negative predictive value (NPV) of 93%, but low PPV thus being used as a **rule out test** to identify benign nodules.[1] Molecular testing is only applicable when combined with clinical and US malignancy features. Study by Kim et al [15] showed that suspicious of malignant cell (SMC) from repeat FNA or *BRAF*V600E mutation in cytopathologic specimen should be a trustworthy surrogate for malignancy and can be considered to proceed with surgery. Absence of US suspicious features combined with less SMC or negative *BRAF*V600E mutation can lead to NPV over 90%. Combination of SMC+ or *BRAF*V600E mutation produce the high positive likelihood ratio, and combination of SMC+ with US malignant features produced the highest [5][14][15].

Surgery was more often recommended in AUS group than FLUS. The risk of malignancy for the nuclear atypia group (32.6%-60%) was significantly higher than that for the microfollicular architecture group (7%-34%) [12]. Some surgeons will prefer early surgical intervention. Early surgery has been recommended in case of male patients aged >40 years and for thyroid nodules with solid components. Surgery in AUS is considered if there are presence of risk in clinical or US, an abnormal repeat FNA and/or abnormal molecular testing result [7] ATA guidelines agree that management decision couldn't be made by cytology alone. Surgical choice for indeterminate thyroid lesion includes hemithyroidectomy, total thyroidectomy or complete removal of thyroid lobes. Hemithyroidectomy remains the gold standard for

definitive diagnosis in AUS cases [16]. Total thyroidectomy has higher complication rates but can be considered in case of significant enlargement of the contralateral lobe, large size of nodule, positive family history, history of radiation, or unwillingness for second surgery. Purpose of surgical management is to obtain a definitive diagnosis. Prophylactic or diagnostic central lymph node dissection is not routinely suggested, but intraoperative frozen section of lymph nodes can be valuable. Completion thyroidectomy may be suggested depend on the final histological diagnosis. Care should be taken to prevent injury in the parathyroid glands and to preserve recurrent and superior laryngeal nerves [16].

Direct surgery after an AUS cytodiagnosis is performed by 15% of physicians in study by Abelardo et al [14] and this is mostly due to a strong malignancy risk of clinical and sonographic features. Wide variation of AUS was seen since 42% physicians received benign histo diagnosis after surgery, and 74% received malignant histologic [14] Other modalities such as Computerized analysis of nuclear images (CANI) also reported beneficial in AUS case. Hayashi et al [17] reported sensitivity and specificity in detecting malignancy that higher than 80% of AUS cases with CANI [17].

In this presented case, we combine the judgement from clinical and risk stratification with USG and CT scan. The 1st case also suggested for surgery due to the upcoming radiation schedule. Surveillance were performed in the 2nd case, and the 6 months follow up showed the nodule that getting bigger thus directly scheduled for surgery with frozen section intra operative. All guidelines are strongly recommended patient involvement in the decision-making and the role of multidisciplinary team discussion for difficult cases. Thus, guidelines emphasize a comprehensive work-up for thyroid nodules, and all available information should be considered before a decision is made [16]. Repeat FNA or molecular testing can be considered to supplement the malignancy risk assessment. However, clinical risk, US risk features and patient preference must be discussed for choosing either close observation or surgery option if the result of repeat FNA or molecular testing is not performed or inconclusive [2].

4. CONCLUSION

Management of AUS is challenging and still debatable since it can present as heterogeneous lesions with different sub classifications according to cytomorphologic and molecular findings. In group of patients with indeterminate nodules, presence of clinical factors such as male, age, family history, history of prior radiation exposure, and increased nodule size, multiply the risk of malignancy and favor surgical management. Considerations of clinical risk stratification, US findings and FNA should be combined altogether for the best management and treatment outcome.

ETHICAL DECLARATION

Authors declared that the patient was consented about publishing his case on the scientific journal.

REFERENCES

[1] Mittal M, Ganakumar V, Shukla R, Garg MK. Thyroid nodule: approach and management.IntechOpen. 2020.DOI: http://dx.doi.org/10.5772/intechopen.91627

[2] Tamhane S, Gharib H. Thyroid nodule update on diagnosis and management. Clinical Diabetes and Endocrinology.2016;2:1-10.

[3] Lee JY, Baek JH, Ha EJ, Sung JY, Shin JH, Kim JH, et al. 2020 imaging guidelines for thyroid nodules and differentiated thyroid cancer: Korean society of thyroid radiology. Korean Journal of Radiology.2021;22:840-860.

[4] Suh YJ, Choi YJ. Strategy to reduce unnecessary surgeries in thyroid nodules with cytology of Bethesda category III (AUS/FLUS): a retrospective analysis of 667 patients diagnosed by surgery. Endocrine;2020; 69:578-586.

[5] Gao LY, Wang Y, Jiang YX, Yang X, Liu RY, Xi XH, et al. Ultrasound is helpful to differentiate Bethesda class III thyroid nodules. A PRISMA-compliant systematic review and meta-analysis. Medicine.2017;96:1-6.

[6] Faquin WC, Baloch ZW. Fine needle aspiration of follicular patterned lesions of the thyroid: Diagnosis, Mangement and follow-up according to National Cancer Institute (NCI) recommendations. Diagnostic cytopathology.2010;38:731-738.

[7] Geramizadeh B, Bos-hagh S, Maleki Z. Cytomorphologic, imaging, molecular findings, and outcome in thyroid follicular lesion of undeermined significance/Atypical cell of undetermined significance (AUS/FLUS): a mini-review. Acta cytologica.2018; doi:10.1159/000493908.

[8] Kim TH, Krane JF. The evolution of “atypia” in thyroid fine-needle aspiration specimens. Diagnostic cytopathology.2021;1-8.

[9] Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid.2017;11:1341-1346.

[10] Yim Y, Baek JH. Core needle biopsy in the management of thyroid nodules with an

indeterminate fine-needle aspiration report. Gland surg.2019;8: S77-S85.

[11] Ogmen BE, Aydin C, Kilinc I, Altinboga AA, Ersoy R, Cakir B. Can repeat biopsies change the prognoses of AUS/FLUS nodule? European thyroid journal.2019;9:92-98.

[12] Choi YJ, Baek JH, Ha EJ, Lim HK, Lee JH, Kim JK, et al. Differences in risk of malignancy and management recommendations in subcategories of thyroid nodules with atypia of undetermined significance or follicular lesion of undetermined significance: the role of ultrasound-guided core-needle biopsy. Thyroid;24: doi:10.1089/thy.2012.0635.

[13] Ryu YJ, Jung YS, Yoon HC, Hwang MJ, Shin SH, Cho JS et al. Atypia of undetermined significance on thyroid fine needle aspiration: surgical outcome and risk factors for malignancy. Annals of surg treatment and research.2014;86:109-114.

[14] Abelardo AD, Sotalbo KCJ. Clinical management of thyroid aspirates diagnosed as atypia of undetermined significance in the Philippines. Gland surgery.2020;9:1788-1796.

[15] Kim TH, Jeong DJ, Hahn SY, Shin JH, Oh YL, Ki CS, et al. Triage of patients with AUS/FLUS on thyroid cytopathology: effectiveness of the multimodal diagnostic techniques. Cancer medicine.2016;5:769-777.

[16] Almquist M, Muth A. Surgical management of cytologically indeterminate thyroid nodules. Gland surg.2019;8: S105-S111.

[17] Hayashi CY, Jaune DTA, Oliveira CC, Coelho BP, Miot HA, Marques MEA, et al. Indeterminate thyroid cytology: detecting malignancy using analysis of nuclear images. Endocrine connections.2021;10:707-714.