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Article type : Original Article

Malignancy Risk for Solitary and Multiple Nodules in Hürthle Cell-Predominant Thyroid Fine Needle Aspirations: A Multi-Institutional Study

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/CNCY.22213

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Running title: ROM of single/multiple Hürthle cell FNAs
Keywords: thyroid, Hürthle cell, FNA, multinodularity, malignancy risk, AUS, FLUS

Abstract

Background: Hürthle cell metaplasia is common in hyperplastic nodules, particularly in the setting of lymphocytic thyroiditis(LT). The Bethesda System for Reporting Thyroid Cytopathology indicates that it is acceptable to classify Hürthle cell-predominant fine needle aspirations(HC FNA) as “Atypia of Undetermined Significance”(AUS) rather than "Suspicious for a Hürthle Cell Neoplasm"(HUR) in the setting of multiple nodules or known LT. The goal of this study is to address whether this approach is justified.

Methods: HC FNAs were identified and correlated with ultrasound(US) and surgical pathology reports if available. Multinodularity was determined by findings on gross examination if imaging results were unavailable.

Results: 698 HC FNAs were identified, including 576 resected nodules of which 455 (79%) were benign. Overall risk of malignancy(ROM) for HUR was 27%, while ROM for AUS was 10%. Mean size of benign nodules was 2.1 cm on resection, with multiple nodules in 293 (64%) and histologic LT in 116 (25%) cases. Mean size of malignant nodules was 2.8 cm, with multiple nodules and histologic LT in 74 (61%) and 22 (18%) cases, respectively. Malignancy rate did not differ between solitary or multiple nodules ($p = 0.52$) or in the presence or absence of LT ($p = 0.12$). However, size did significantly differ between malignant and benign nodules ($p < 0.01$).

Conclusion: The malignancy rate did not significantly differ in the presence of multiple nodules or LT, although the latter showed a statistical trend. A diagnosis of AUS over HUR based solely on the presence of multinodularity is not warranted.

Condensed abstract

The malignancy rate for Hürthle cell-predominant thyroid FNAs does not significantly differ in the presence of multiple nodules or lymphocytic thyroiditis, although the latter shows a statistical trend. A diagnosis of "atypia of undetermined significance" over "suspicious for a Hürthle cell neoplasm" based solely on the presence of multinodularity is not warranted.

Introduction

Hürthle cells are modified thyroid follicular cells which demonstrate oncocytic change, resulting in abundant eosinophilic granular cytoplasm due to the presence of numerous mitochondria[1]. They are often associated with enlarged, round nuclei and central prominent nucleoli. Although oncocytic/Hürthle cell change was initially thought to be secondary to senescence, it is now thought to be a metaplastic change in response to cellular stress or changes in the microenvironment[1]. Hürthle cell metaplasia may be seen in a variety of non-neoplastic conditions such as autoimmune thyroiditis (including Hashimoto thyroiditis and Graves' disease) and multinodular hyperplasia, although it can also be seen in both benign and malignant neoplasia.

Given this lack of specificity of Hürthle cell metaplasia, accurate diagnosis of Hürthle cell-predominant fine needle aspirations (HC FNA) can be extremely problematic. Many cytologic features have been proposed for distinguishing non-neoplastic Hürthle cell nodules from neoplastic nodules as well as benign from malignant nodules, although no criteria have been widely accepted. These include cellularity[2–5], amount of colloid[2–4,6–8], architecture (i.e. macrofollicular sheets, crowded groups, singly dispersed cells)[3–5,7,8], and nuclear pleomorphism or "dysplasia"[2,3,5–9], among others. Given the inconsistency of cytologic features in the evaluation of HC FNA, it has also been suggested in The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) that clinicopathologic correlation can aid in evaluation. Specifically, TBSRTC states that it is acceptable to classify HC FNA as "Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance" (AUS/FLUS) rather than "Suspicious for a Hürthle Cell Neoplasm" (HUR) in the setting of multiple nodules or known lymphocytic thyroiditis[10]. The goal of this study is to address whether this approach is justified.

Materials and Methods

Study Population and Data Acquisition

Approval from the institutional review board from each participating institution was obtained. A search of Hürthle cell-predominant fine needle aspirations (HC FNA) was performed at each institution. Thyroid FNA cytologic preparations varied across institutions as well as within individual institutions (i.e. due to operator preference), ranging from routine use of both smear preparations (Diff-Quick- or Papanicolaou-stained) and liquid-based preparations to use of only one method. Cytologic diagnoses and patient demographics were recorded for each case. HC FNA were categorized using The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) using the following diagnostic categories: Benign, Atypia of Undetermined Significance (AUS), Suspicious for a Hürthle Cell Neoplasm (HUR), Suspicious for Malignancy (SUS), and Malignant.

When available, nodule size and the presence or absence of multiple nodules were documented from ultrasound (US) reports. Surgical pathology reports from cases with surgical follow-up

were reviewed. Multinodularity was determined by findings on gross examination if imaging results were unavailable. The histologic diagnosis, including presence of lymphocytic thyroiditis, was also recorded for each case.

Surgical pathology diagnoses were classified using a binary system, i.e. "benign" or "malignant". All cases in this study pre-dated the introduction of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), and cases which had been diagnosed as follicular variant of papillary thyroid carcinoma (FVPTC) or PTC in which the subtype was not specified (PTC, NOS) were not re-classified. These cases were included in the "malignant" category for the purposes of this study, as the goal was to differentiate benign lesions from those that would require surgical resection in the setting of multinodularity.

Statistical Analysis

A *t*-test or Fisher exact test was used to compare differences in continuous and categorical variables, respectively (Prism 5, GraphPad, La Jolla, CA). For all statistical methods, *p*-values <0.05 were considered significant.

Results

Cohort Characteristics

Overall, 698 HC FNA from 677 nodules were identified. The FNA diagnosis was Benign in 12 (2%) cases, AUS in 275 (39%) cases, HUR in 407 (58%) cases, Suspicious for Malignancy in 3 (<1%) cases, and Malignant in 1 (<1%) case. Five hundred seventy-six (85%) nodules were resected. Characteristics of resected and unresected cases were compared in a subset of cases where sufficient information for the unresected nodules was available from the participating institutions (summarized in Table 1). Patients who did not undergo surgical resection were more likely to be older ($p = 0.021$) and have a preceding Benign or AUS diagnosis ($p = 0.011$ and 0.0075, respectively), while those with a preceding HUR diagnosis were more likely to undergo resection ($p = 0.0017$). There was no significant difference between resected and unresected cases in ultrasonographic size of the nodule, presence of multinodularity, or the presence of multiple HC nodules sampled on FNA.

The clinicopathologic features of all 576 cases which underwent resection are summarized in Table 2. Of resected nodules, 455 (79%) were classified as benign and 121 (21%) malignant. Sonographic assessment of multinodularity was available in 342 (59%) resected nodules overall, including 257 of 454 (56%) benign nodules and 79 of 121 (65%) malignant nodules. Gross assessment of multinodularity was available in the remaining cases. The incidence of multinodularity was not significantly different between nodules with sonographic or gross assessment (65% and 62%, respectively; $p = 0.48$).

Benign Nodules

Of patients with benign nodules, 368 (83%) were female and 77 (17%) male. The mean age of patients was 54 years old (range: 19-88). The preceding FNA diagnosis was Benign in 5 (1%) cases, AUS in 189 (42%) cases, HUR in 260 (57%) cases, Suspicious for Malignancy in 1 (<1%) case, and Malignant in 0 (0%) cases. All 10 patients who had more than one nodule with a preceding HC FNA had benign findings on resection. The mean size of benign nodules was 2.3 cm by US and 2.1 cm on resection. Multiple nodules were identified in 293 (64%) cases overall, including 168 of 261 (64%) which had sonographic assessment available and 126 of 194 (65%) which were evaluated grossly. On histopathologic examination, there were 264 (58%) follicular adenomas or adenomatous nodules (Figure 1), 166 (36%) hyperplastic nodules, 2 (<1%) infarcted nodules, 1 (<1%) hyalinizing trabecular tumor, and 1 (<1%) parathyroid adenoma. The remaining 21 (5%) cases demonstrated only LT without a dominant nodule documented, although 116 (26%) cases overall had histologic LT.

Malignant Nodules

The mean age of patients with malignant nodules was 55 (range: 15-87), with 94 (77%) females and 28 (23%) males. The preceding FNA diagnosis was Benign in 2 (2%) cases, AUS in 21 (17%) cases, HUR in 95 (79%) cases, Suspicious for Malignancy in 2 (2%) cases, and Malignant in 1 (1%) case. Compared to benign nodules, malignant nodules were more likely to have been diagnosed as HUR on FNA ($p < 0.01$) (see Table 2). The overall risk of malignancy (ROM) for HUR was 27% (95/355), while the ROM for AUS was 10% (21/210).

The mean size of nodules was 2.8 cm on both US and resection. Sonographic and histopathologic sizes were significantly different between malignant and benign nodules (both $p < 0.01$). Of malignant nodules, there were 65 (54%) follicular carcinomas (including Hürthle cell carcinomas), 47 (39%) PTC, 6 (5%) poorly differentiated thyroid carcinomas (Figure 2), 2 (2%) medullary carcinomas, and 1 (1%) undifferentiated carcinoma. Of PTC cases, 24 (20%) were FVPTC, 16 (13%) were non-follicular variant (including classical, oncocytic, and solid variants), and 7 (6%) did not have a subtype specified (PTC, NOS). Twenty-two (18%) cases demonstrated histologic LT. Multiple nodules were detected in 74 (61%) cases overall. These included 54 of 81 (67%) nodules which had US evaluation available and 19 of 40 (48%) which were evaluated grossly. Among the entire cohort, there was not a statistically significant difference in the malignancy rate in the presence or absence of LT, although there was a weak statistical trend ($p = 0.12$). Malignancy rate also did not differ in the setting of solitary or multiple nodules ($p = 0.52$) or when considering concurrent multinodularity and LT ($p = 0.77$).

Discussion

Hürthle cell metaplasia is common in thyroid nodules and can be seen in both malignant and benign thyroid disease, including non-neoplastic conditions such as LT or multinodular hyperplasia. For this reason, evaluation of HC FNA can be challenging, especially given the lack of specificity of morphologic features in identifying neoplasia or differentiating benign from malignant nodules in cytologic preparations. To aid in this differential, TBSRTC has recommended that clinical features can be useful in evaluation of HC FNA. In particular, TBSRTC has offered that it is acceptable to diagnosis HC FNA has AUS/FLUS rather than HUR in a patient with multiple thyroid nodules or LT[10].

In this multi-institutional study, we evaluated a large cohort of HC FNA in order to determine whether this approach suggested by TBSRTC is justified. Overall, we found that 79% of the 576 resected Hürthle cell-predominant nodules were benign, while the remaining 21% were malignant. More specifically, the ROM for HC FNA diagnosed as HUR was 27%, while that of AUS was 10%. The ROM for AUS with a predominance of Hürthle cells (AUS-HC) and HUR have been highly variable in the literature, with rates ranging from 0%-26% for AUS-HC[11–16]

and 14-45% for HUR[2,6,7,15,17–28]. However, the median ROM for AUS-HC and HUR among these studies are 11% and 23%, respectively, similar to findings we observed in our cohort. Our study did not specifically address the underlying rationale for classifying thyroid aspirates as AUS-HC rather than HUR. Our findings indicate that the number of nodules present should not determine this distinction; however, other parameters such as overall cellularity, abundance of colloid and cell cohesiveness undoubtedly factor into classification of Hürthle cell nodules and are able to stratify such lesions to a limited extent.

Among benign nodules, we found that the incidence of multinodularity was 64% compared to 61% in malignant nodules ($p = 0.52$). Prior studies evaluating the significance of multinodularity in HC FNA have been limited. However, one study by Turanli *et al.* did not find a significant difference in multinodularity in benign (53%) and malignant (43%) disease[29]. Another study by Sclabas *et al.* evaluated multinodularity in the setting of all indeterminate FNA, where again no difference was found in malignant nodules[22]. In histologic evaluation of follicular neoplasms, including both Hürthle and non-Hürthle cell lesions, the number of nodules has been associated with malignancy risk[23]. Amongst all thyroid nodules, however, the significance of multinodularity on ROM has been highly variable in the literature. In a meta-analysis of 14 studies, a slightly lower ROM was seen in the setting of multinodular goiter, although this difference was seen only when including studies outside the United States from iodine-deficient areas[30]. Although we found no overall difference in ROM between Hürthle cell nodules in solitary or multinodular thyroids, all 10 patients in our cohort who had more than one nodule with a preceding HC FNA had benign findings on resection. This finding in a limited number of cases did not reach the level of statistical significance, but at least raises the possibility that an AUS-HC diagnosis may be warranted in the circumstance of a patient with multiple Hürthle-cell rich nodules (vs. multiple non-Hürthle cell or just radiographically detected nodules). A caveat to this, however, is that there could potentially be sampling of "multiple" nodules which in fact are different areas of a single large and/or irregular lesion or a multifocal tumor. Although close radiologic correlation may help with this distinction, in some cases the distinction may not always be possible. A larger series of such cases is needed to further examine this specific uncommon scenario.

Additionally, in our study we also evaluated the rate of histologic LT among benign nodules (26%) compared to malignant nodules (18%), although the difference we observed did not reach significance (p = 0.12). This finding is similar to prior studies, which also did not find a difference in LT among benign and malignant nodules with preceding HC FNA[19,31]. In the study by Canberk *et al.*, histologic LT was identified in 53/213 (25%) thyroids with benign nodules and 14/56 (25%) malignant thyroids[31]. Roh *et al*., who included both clinical, radiologic, and histologic criteria for Hashimoto thyroiditis, also did not find a statistical difference in ROM of nodules with a preceding HUR FNA (25.2 vs 9.5%; p =0.081)[19]. However, given that the ROM for cases without Hashimoto thyroiditis more closely approached the expected ROM for AUS/FLUS[10], the authors suggest that it may be more appropriate to diagnose these HC FNA cases as AUS/FLUS rather than HUR[19]. When using only cytologic findings in HC FNA suggestive of LT (i.e. markedly increased lymphocytes), there have also been variable results in predicting ROM for HC FNA[2,9]. Although not the primary focus of the current study, our data reinforces the notion that the impact of LT on ROM for Hürthle cell-rich aspirates is limited, showing only a weak statistical trend not rising to the level of statistical significance in multiple studies. Nevertheless, even a minimal impact on ROM in the setting of LT is consistent with favoring an AUS diagnosis over HUR in this context.

Limitations of this study include variability in our assessment of multinodularity. While most cases had imaging results available, a subset of cases relied on gross pathologic examination, and it is unclear whether the latter would have had clinically or radiologically detectable multinodularity at the time of FNA. Limitations in data availability also prohibited further assessment of more granular findings, such as number and size of additional thyroid nodules. Additionally, because our criterion for LT included only histologic examination, we may not have captured cases with reporting bias (i.e. LT present but not documented in the surgical pathology report). Additionally, histologic LT can be a somewhat non-specific finding and is, of course, only known following resection. The inclusion instead of patients with true autoimmune thyroiditis or convincing radiologic evidence of thyroiditis may be more clinically relevant. However, limited access to detailed information in the patient medical record served as a barrier to more complete characterization of these patients. Finally, given that there was not central review of cytology slides, there was likely some variability in criteria for FNA diagnosis

between institutions as well as individual cytopathologists. Subjectivity in what constitutes a predominance of Hürthle cells beyond what is acceptable for benign/reactive conditions could have affected the AUS threshold and overall case selection. However, pooling of data from all institutions may have minimized any potential biases in diagnostic criteria.

In conclusion, we found that multinodularity and LT were not significantly different in benign and malignant Hürthle cell-predominant nodules (including cases that are now classified as NIFTP, which still require surgical resection). Our large multi-institutional data set suggests that the option in TBSRTC for downgrading HC FNA from HUR to AUS solely on the basis of multinodularity is generally unwarranted. The specific scenario of multiple Hürthle cell nodules may represent an exceptional circumstance warranting further study along with other factors contributing to risk stratification among Hürthle cell-rich thyroid aspirates.

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Figure Legends

Figure 1: Example of a benign nodule in our cohort. The preceding FNA had abundant Hürthle cells singly dispersed and in clusters (A). The surgical resection demonstrated an adenomatous nodule with Hürthle cell change (B, C).

Figure 2: Example of a malignant nodule. The FNA was composed of cells with abundant oncocytic cytoplasm, round nuclei, and prominent nucleoli (A). The subsequent resection revealed a widely invasive poorly differentiated thyroid carcinoma (B, C).

Table 1. Clinicopathologic Characteristics of Resected vs. Unresected Nodules [a]

Characteristic	Resected Nodules (n = 309) [a]	Unresected Nodules (n = 93) [a]	P-value
Sex [n (%)]			
Female	237 (79)	75 (82)	0.77
Male	62 (21)	17 (18)	
Age (years)			
Mean	55	59	0.021
Range	19-88	14-87	
FNA diagnosis [n (%)]			
Benign	1 (<1)	4 (4)	0.011
AUS	110 (36)	48 (52)	0.0075
HUR	194 (63)	41 (44)	0.0017
SUS	3 (1)	0 (0)	1.0
Malignant	1 (<1)	0 (0)	1.0
Mean tumor size: ultrasound (cm)	2.4	2.3	0.39
Nodularity [n (%)] [b]			
Multiple	202 (66)	52 (65)	0.89
Single	103 (34)	28 (35)	
HC FNA of >1 nodule [n (%)]	10 (3)	1 (1)	0.47

[a] Only information from a subset of unresected cases was available for comparison.

[b] Of patients with ultrasound findings available.

AUS: atypia of undetermined significance; HUR: Suspicious for a Hürthle cell neoplasm; SUS: suspicious for malignancy; HC FNA: Hürthle cell-predominant fine needle aspiration.

Table 2. Clinicopathologic Characteristics of All Resected Nodules

Characteristic	All Resected Nodules (n = 576)	Benign (n = 455)	Malignant[a] (n = 121)	p-value
Sex [n (%)]				
Female	462 (82)[b]	368 (83)[b]	94 (78)	0.23
Male	104 (18)[b]	77 (17)[b]	27 (22)	
Age (years)				
Mean	54	54	55	0.47
Range	19-88	19-88	15-87	
FNA diagnosis				
Benign	7 (1)	5 (1)	2 (2)	0.64
AUS	210 (36)	189 (42)	21 (17)	<0.01
HUR	355 (62)	260 (57)	95 (79)	<0.01
SUS	3 (<1)	1 (<1)	2 (2)	0.12
Malignant	1 (<1)	0 (0)	1 (1)	0.21
HC FNA of >1 nodule [n (%)]	10 (2)	10 (2)	0 (0)	0.13
Mean tumor size: ultrasound (cm)	2.5	2.3	2.8	<0.01
Mean tumor size: gross (cm)	2.2	2.1	2.8	<0.01
Nodularity [n (%)][c]				
Multiple	367 (64)	293 (64)	74 (61)	0.52
Single	209 (36)	162 (36)	47 (39)	
LT [n (%)]				
Present	138 (24)	116 (25)	22 (18)	0.12
Absent	438 (76)	339 (75)	99 (82)	
Concurrent MN and LT [n (%)]				
Present	84 (15)	68 (15)	16 (13)	0.77

Absent	492 (85)	387 (85)	105 (87)

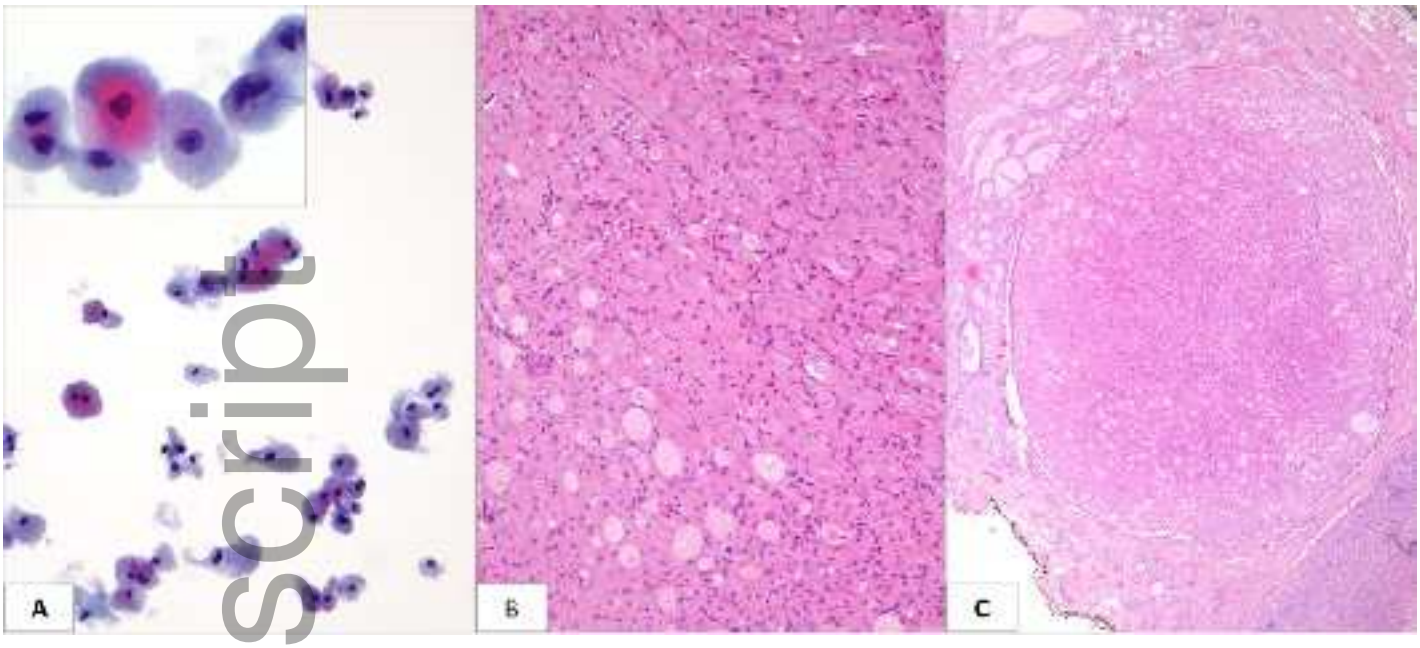
p-values are based on comparison of benign and malignant nodules.

[a] All non-benign nodules were included in this group, including cases previously diagnosed as follicular variant of papillary thyroid carcinoma (see Methods).

[b] Ten patients had 2 different nodules with a preceding Hürthle cell-predominant fine needle aspiration.

[c] Multinodularity was determined by ultrasound or gross findings.

AUS: atypia of undetermined significance; HUR: Suspicious for a Hürthle cell neoplasm; SUS: suspicious for malignancy; MN: multinodularity; LT: lymphocytic thyroiditis.



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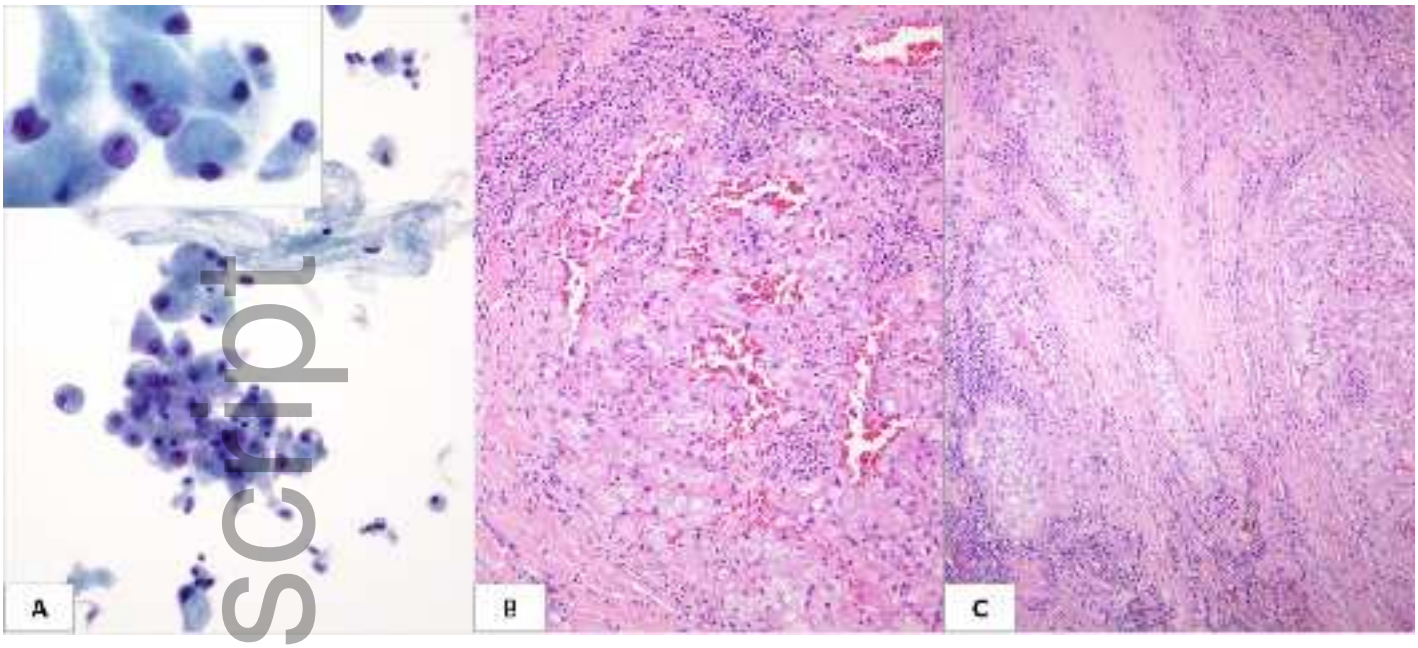

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