DR. SWATI SATTURWAR (Orcid ID : 0000-0003-1960-9847)

DR. ESTHER DIANA ROSSI (Orcid ID : 0000-0003-3819-4229)

DR. ZAHRA MALEKI (Orcid ID : 0000-0003-3273-4802)

DR. WILLIAM C FAQUIN (Orcid ID : 0000-0002-9043-7171)

DR. LIRON PANTANOWITZ (Orcid ID : 0000-0001-8182-5503)

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TITLE PAGE

Thyroid Paraganglioma: A Diagnostic Pitfall in Thyroid FNA

Swati P Satturwar MD[1], Esther D Rossi MD, PhD[2], Zahra Maleki MD[3], Richard L Cantley MD[4], William C Faquin MD PhD[5], Liron X Pantanowitz MD[1,4]

1. Department of Pathology, University of Pittsburgh, PA, USA

2. Department of Pathology, Catholic University-Fondazione Policlinico Universitario, Rome, Italy

3. Department of Pathology, Johns Hopkins Hospital, Baltimore, MD, USA

4. Department of Pathology, University of Michigan, Ann Arbor, MI, USA

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5. Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

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Condensed Abstract: Thyroid paragangliomas are extremely rare and often misdiagnosed by pre-operative fine needle aspiration (FNA) cytology. The presence of naked nuclei, focal marked anisonucleosis, sustentacular cells, and absence of colloid are important cytologic clues that may help to triage FNA samples for ancillary testing to confirm the diagnosis.

For correspondence: Liron Pantanowitz, MD, Department of Pathology, University of Michigan, MCRC Bldg 25, 2800 Plymouth Road, Ann Arbor, MI, USA. Email: lironp@med.umich.edu

ABSTRACT

Background: Thyroid paragangliomas are extremely rare and often misdiagnosed by pre-operative fine needle aspiration (FNA) as their cytologic features overlap with other thyroid neoplasms. The aim of this study was to review the cytomorphology in a series of thyroid paragangliomas and correlate the findings with histopathology.

Materials and Methods: Five thyroid paraganglioma cases that underwent FNA were reviewed. Their clinical presentation, radiology features, cytomorphology, ancillary tests, and histopathology were analyzed.

Results: All patients were female of average age 49 years (range 35-61 years) and presented with an asymptomatic, solitary thyroid nodule. Radiologically these nodules (1.8 to 3.0 cm) were well-circumscribed, hypoechoic, and hypervascular. FNA smears showed clusters of loosely

cohesive, medium to large epithelioid cells with clear to eosinophilic and occasionally foamy cytoplasm with indistinct cytoplasmic borders. The nuclei were round to oval with focal nuclear membrane irregularities, inconspicuous nucleoli, focal marked anisonucleosis and occasional intranuclear pseudoinclusions. Naked nuclei, variable numbers of plasmacytoid cells, multinucleated giant cells and sustentacular cells were present in the background along with blood vessels and lymphocytes. Cytology diagnoses were incorrect and included follicular neoplasm (n=4) and follicular lesion of undetermined significance (n=1). Final histopathology with immunohistochemistry showed a conventional paraganglioma (n=3) or sclerosing paraganglioma with invasive features (n=2).

Conclusions: All thyroid paragangliomas were misdiagnosed on FNA as follicular neoplasms in part due to the rarity of these tumors in this location, and cytomorphology mimicking follicles. Absence of colloid, presence of naked nuclei, focal marked anisonucleosis, and the presence of sustentacular cells are important cytology clues.

Key words: Cytopathology, cytomorphology, fine needle aspiration (FNA), paraganglioma, sclerosing paraganglioma, thyroid

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INTRODUCTION

Paragangliomas are slow growing neuroendocrine tumors that originate from neural crest-derived paraganglia and are considered to represent an extra-adrenal counterpart of pheochromocytoma. They can be found anywhere in the human body from the base of the skull to the pelvis, along the embryologic migration routes of neural crest cells.[1] They can be familial or sporadic and predominantly affect women (F:M=2-3:1) between 40-60 years of age.[1,2] These tumors can be functional, producing hormones like adrenalin and noradrenalin that can cause transient or permanent hypertension. Measuring serum or urinary catecholamines and their end

products such as vanillylmandelic acid (VMA) can be helpful for the diagnosis of functional tumors.[3,4] Due to the potential for a hypertensive crisis and intra-procedural hemorrhage/bleeding, fine needle aspiration (FNA) of these tumors is generally discouraged.

All head and neck paragangliomas arise from parasympathetic paraganglia and account for 0.6% of the all head and neck tumors. The most common location in this region is the carotid body, followed by the jugular bulb. Thyroid paragangliomas are extremely rare, and are considered to be a subset of inferior laryngeal paragangliomas. As opposed to pheochromocytomas, most thyroid paragangliomas are non-functional and present as asymptomatic solitary thyroid nodules that are often considered to be primary thyroid neoplasms and therefore likely to be evaluated by FNA. These tumors pose a diagnostic challenge by cytologic and histologic evaluation not only because of their rarity in this anatomic location, but also due to their morphologic overlap with benign and malignant thyroid neoplasms as well as metastatic neuroendocrine tumors.[5-9] In particular, the sclerosing variant of paraganglioma can have unusual morphology with extensive sclerosis that may simulate an invasive malignant neoplasm.[10]

The aim of this study was to review the clinical presentation and cytomorphologic spectrum of thyroid paragangliomas and correlate these findings with histopathology on follow-up resection.

MATERIALS AND METHODS

A retrospective review of 5 thyroid paraganglioma FNA cases was performed. The cases were collected from the University of Pittsburgh Medical Center, Pittsburgh, PA, USA (n=2), Catholic University-Fondazione Policlinico Universitario, Rome, Italy (n=1), Johns Hopkins Hospital, Baltimore, MD, USA (n=1) and the Massachusetts General Hospital, Boston, MA, USA (n=1).

These FNAs were performed by radiologists or endocrinologists under ultrasound guidance. Rapid onsite evaluation (ROSE) was performed in 2 cases. Air dried and alcohol-fixed direct smears were prepared from each pass until the material was deemed adequate for diagnosis or the procedure was terminated. The air-dried slides were stained with a Romanowsky-type stain (Diff-Quik) and the alcohol-fixed slides were stained with a Papanicolaou stain. Material was collected for liquid based preparation (ThinPrep) in three cases. Cell blocks were not prepared for any of these cases. Aspirated material was collected for ancillary molecular studies for 2

cases in ThyroSeq*Preserve* medium. The final cytology reports were signed out by board certified cytopathologists. Follow-up surgical resection glass slides and/or digital slides (scanned at 40x using an Aperio AT2 whole slide scanner, Leica) were reviewed for correlation with the FNA findings. Immunohistochemistry was performed on the surgical resection in all 5 cases with appropriate positive and negative controls.

The available metadata collected included patient demographics, radiology findings, and follow-up clinical information. Cytomorphology details including the type of specimen preparation utilized, cellularity, pattern, cell size/shape, cytoplasm, nuclear features, background, as well as the Bethesda category, and final cytology diagnosis were recorded. Cytopathology-histopathology correlation was performed in all cases and the results of available ancillary tests (immunohistochemistry and molecular) were documented.

RESULTS

Clinical Findings

All patients were women (n=5) and presented with an asymptomatic thyroid nodule. One case (case 3) was detected incidentally on a CT scan of the head and neck region while working up this patient for a right vagus nerve schwannoma. The average age at presentation was 49 years (range 35-61years). Radiologically, these nodules were well-circumscribed, hypoechoic, and hypervascular, and they ranged in size from 1.8 to 3.0 cm. The nodules involved the left thyroid lobe (n=4) with extension into the isthmus in one case, and the right thyroid lobe (n=1). The clinical, radiologic and available genetic test findings from FNA material are summarized in **Table 1**. Pre-operative biochemical testing of serum or urine hormonal levels was not performed as these patients were asymptomatic, except for case 5 where the patient had a history of hypertension. The clinical diagnosis of paraganglioma was not suspected in any of these cases. On post-operative follow-up, a complete clinical work-up was negative for multicentric disease. In case 5, a small partially calcified portocaval mass was detected. **Table 2** summarizes the FNA and surgical procedure details.

Cytopathology and Molecular Findings

The spectrum of cytopathologic findings is summarized in **Tables 3 and 4**. In case 2, an initial FNA was reported as atypia of undetermined significance (AUS) with a negative ThyroSeq molecular test. A follow-up FNA for case 2 performed 6 months later was reported as a follicular neoplasm with a negative ThyroSeq molecular test, but positive SDHB mutation. For case 3, an initial FNA was non-diagnostic which was followed by a repeat FNA 2 months later with an AUS diagnosis. ThyroSeq test was reported as indeterminate due to insufficient material. For case 5, in which an initial FNA was reported as AUS 3.5 months earlier, a repeat FNA was classified as suspicious for a follicular neoplasm.

FNA smears were hypocellular (n=3) or hypercellular (n=2). Smears showed clusters of loosely cohesive and isolated epithelioid cells, with round to oval morphology, medium to large in cell size and with clear, amphophilic to foamy cytoplasm with indistinct cytoplasmic borders. Scattered plasmacytoid cells were present in two cases. (**Figure 1**) The nuclei were round to oval with focal nuclear membrane irregularities, grooves, inconspicuous nucleoli and occasional intranuclear pseudoinclusions. (**Figures 2-3**) Scattered cells with marked anisonucleosis were present in all cases (**Figure 4**). Naked nuclei were present in four cases. Variable binucleated and multinucleated giant cells were also present. The background showed blood vessels (**Figure 5)**, red blood cells and lymphocytes without colloid or amyloid. A few possible sustentacular cells with oval, elongated curved naked nuclei were present in 2 cases. The sclerosing variant showed tight cohesive clusters of spindle to epithelioid cells with overlapping nuclei on liquid based preparation (**Figure 6**). The cytopathology diagnoses rendered were follicular neoplasm (n=3), suspicious for follicular neoplasm (n=1) and AUS/follicular lesion of undetermined significance (FLUS) (n=1).

Histopathology Findings

All thyroid lesions were surgically excised. The final surgical diagnoses were paraganglioma (n=3) and sclerosing paraganglioma with invasive features (n=2). Intra-operative frozen section diagnoses were available for 3 cases and reported as follows: (case 3) follicular lesion, (case 4) cellular lesion, defer to permanent section, and (case 5) suspicious for medullary thyroid carcinoma (MTC). The histopathology (cases 1, 4 and 5; **Figure 7 A-C**) was similar to

pheochromocytoma or other anatomic site paragangliomas. These tumors were composed of nests of tumor cells (Zellballen) or growing in a trabecular pattern associated with a prominent vascular network. The cells were round to oval with abundant granular eosinophilic or basophilic cytoplasm. The nuclei were round to oval with scattered severe anisonucleosis. There were occasional giant multinucleated cells observed. Rosettes, acini, melanin pigment, necrosis, mitoses, and vascular or capsular invasion were not present.

Cases 2 and 3 showed features of sclerosing variant of paraganglioma **(Figure 8 A-D).** In these two cases, on gross examination of the resected thyroid specimen the cut surface revealed a solid, pink-tan ill-defined mass. Histopathology of the sclerosing variant of paraganglioma was characterized by a focal nested Zellballen growth pattern admixed with irregular, highly sclerotic and vascularized bands of stroma separating tumor nests. The tumor cell nuclei in these sclerosing tumors showed focal nuclear atypia including some large cells with prominent nucleoli and scattered hyperchromatic nuclei. The cells were spindle to epithelioid and their cytoplasm was clear to granular and foamy, imparting a histiocytoid appearance. Infiltrative growth was evident as extensive sclerosis at the periphery with positive surgical resection margins and involvement of perithyroidal skeletal muscle. Unlike conventional paragangliomas, the thick sclerotic and fibrous bands of sclerosing paragangliomas imparted the appearance of desmoplastic stroma typically seen with invasive malignant neoplasms. Rare atypical mitoses were present in one case. Both sclerosing paraganglioma cases showed scattered tumor infiltrating lymphocytes but no necrosis, and no capsular nor vascular invasion was present. Background chronic lymphocytic thyroiditis was present in four cases. Case 4 also had an incidental papillary microcarcinoma (0.2 cm).

Immunohistochemistry Findings

Immunohistochemistry was performed on all 5 surgical resection specimens. The tumor cells were positive for synaptophysin and/or chromogranin. S-100 highlighted the sustentacular cells and nearby nerves and CD34 highlighted the rich tumor vascular network. The tumor cells were negative for pancytokeratin, TTF-1, thyroglobulin, calcitonin, CEA and HBME. Case 2 showed loss of SDHB by immunohistochemistry.

Follow-up

For case 1 the patient did well without any recurrence or metastatic disease 7 years following surgery. In case 2 the patient developed temporary post-operative laryngeal nerve paralysis and hoarseness that resolved after 6 months. For this patient, at follow-up ultrasound 8 years after surgery a 0.6 cm possible remnant was discovered in the thyroid bed that is being followed-up radiologically due to its small size for further investigation. For cases 3, 4 and 5 these patients all did well without recurrence or metastatic disease even up to 9 years after surgery. In case 5 the patient's hypertension was not resolved after surgical resection, confirming the non-functional nature of her thyroid paraganglioma.

DISCUSSION

Thyroid paragangliomas, related to the fact that they are very rare neoplasms in this anatomic location, are usually misdiagnosed by FNA. In our series, all cases were misdiagnosed by cytology (5/5), as well as at frozen section (3/3). Normal paraganglia act as chemoreceptors and thereby play an important role in homeostasis by secreting catecholamines in response to stress. Paraganglia are made up of two cell types: type 1 (chief) and type 2 (sustentacular) cells. Type 1 cells contain cytoplasmic granules filled with catecholamines, while type 2 cells act as supporting cells. Paraganglia can also be categorized into two physiologic groups: (i) parasympathetic, arising mostly in the head and neck region, which are usually non-functional, and (ii) sympathetic, arising in the retroperitoneum, mediastinum or pelvis, which are usually functional.[1,2,11] Paragangliomas may arise from these paraganglia and are typically benign, slow growing tumors. Possible etiologies for their development include chronic hypoxic exposure and heritable causes such as mitochondrial complex II defects. In our series, 4 of the 5 cases also had chronic lymphocytic thyroiditis. The significance of this association is unknown, which to the best of our knowledge has not been previously reported in the literature.

Although the majority or paragangliomas are sporadic, a significant number of cases can be familial. The familial syndromic cases tend to be multicentric and prone to recurrence. Germline mutation testing is hence recommended for all patients with paragangliomas. A positive family history is found in 10-25% cases with germline mutations in SDHD, SDHB and SDHC. While SDHD mutation is the most common, SDHB is associated with a poorer prognosis. In our small series SDHB mutation was detected in one case (case 2), which is interestingly the only patient with possible local recurrence. Occasional cases may also be observed in association with von Hippel-Lindau disease, multiple endocrine neoplasia type 2 (MEN2) and neurofibromatosis, as well as with Carney's triad (gastrointestinal stromal tumor, paraganglioma and pulmonary chondroma).[12,13] Head and neck paraganglia, including those located in the thyroid, typically lack endocrine activity, except for the carotid body paraganglia which possess endocrine activity and contain catecholamines. Consequently, they often present as asymptomatic slow growing masses in the neck without a hypertensive crisis or circulating catecholamines.

Based on limited published cases, the clinical course of thyroid paragangliomas is variable with the majority behaving in a benign fashion and occasionally with local aggressive behaviour.[14,15] In our small series the clinical outcomes after surgery were all favorable. Only 3 case reports of malignant paraganglioma of the thyroid have been described in the literature.[16-18] Surgical resection is the treatment of choice for symptomatic thyroid paragangliomas, after which patients require prolonged follow-up with imaging. Although FNA of a paraganglioma is allegedly contraindicated, it can be performed if biochemical screening for catecholamine secretion is negative and the patient is prepared with alpha adrenergic blockade. Since the pre-operative diagnosis was not suspected in any of our cases FNA was performed without such blockade. Fortunately, the tumors in our series were non-functional and the FNA procedures occurred without any acute adverse event.

The cytopathologic features of thyroid paragangliomas are similar to paragangliomas at other anatomic sites. These features overlap with primary benign and malignant neoplasms of the thyroid gland, parathyroid neoplasms, and metastatic neuroendocrine tumors leading to diagnostic challenges.[19-21] In our series, most of the FNA specimens were misdiagnosed as a

follicular neoplasm. This was likely attributed to their pattern of loosely cohesive clusters of round cells that mimicked follicles. The unique constellation of cytologic features evident in our series that may be diagnostically helpful include clusters of round epithelioid cells in association with focal marked anisonucleosis, sustentacular cells, naked (stripped) nuclei and the absence of background colloid or amyloid. Thyroid paragangliomas may also be misdiagnosed as MTC due to the presence of plasmacytoid or spindle cells, multinucleated giant cells and intranuclear inclusions. Collecting material for cell block to perform immunohistochemistry is essential for reaching the correct diagnosis (**Table 5**), in addition to measuring serum calcitonin and carcino-embryonic antigen (CEA) levels. By immunohistochemistry, both paragangliomas and MTC show expression of neuroendocrine markers. However, MTC would also be positive for calcitonin and CEA. Furthermore, a Congo red stain for suspected amyloid would only be positive in MTC. It is important to note that the paraganglioma-like variant of MTC would be negative for calcitonin, complicating the distinction.[22]

In hyalinizing trabecular tumor (HTT), also known as paraganglioma-like adenoma of thyroid, the cytopathology is characterized by small loose clusters or syncytia of bipolar or triangular cells. The follicular cells in HTT often have more filamentous cytoplasm with long cytoplasmic processes surrounding amorphous basement membrane material. The nuclei in HTT are round to elliptical with smooth borders, have even chromatin and can have intranuclear inclusions and grooves. The amorphous basement membrane material can mimic amyloid of MTC. By immunohistochemistry, HTT is positive for TTF-1, thyroglobulin, PAX-8 and shows membranous expression of Ki-67.[23] Intranuclear pseudo-inclusions could also confuse a paraganglioma with papillary thyroid carcinoma. However, cytologic features such as papillary fragments, nuclear grooves, psammoma bodies, and dense gum-like colloid would help support the diagnosis of papillary thyroid carcinoma. By immunohistochemistry, papillary thyroid carcinoma would be positive for TTF-1, thyroglobulin, PAX-8, CK19 and HBME whereas a paragangliomas would be negative.[23]

Of note, most thyroid paragangliomas may also be misdiagnosed on intra-operative frozen sections as follicular carcinoma, Hürthle cell carcinoma, MTC, metastatic carcinomas or end up being deferred.[25,26] Three cases in our case series that had an intra-operative frozen section were

incorrectly reported as a follicular lesion, cellular lesion best deferred to permanent sections, and suspicious for MTC. Like cytology, conventional paragangliomas show similar histopathology to paragangliomas in other anatomic sites. Unusual morphologic variants such as the sclerosing variant[10,27,28] can exhibit a hemangiopericytoma-like appearance and show clear cell changes as well as spindling of cells. Sclerosing paragangliomas can be symptomatic, sometimes causing airway occlusion as reported by Mukhopadhyay et al.[10] The presence of extensive sclerosis may simulate an invasive histologic growth pattern that mimics malignancy. The sclerosing variant is also known for recurrence. The differential diagnosis of sclerosing paraganglioma in the thyroid includes fibrous variant of Hashimoto thyroiditis, Reidel thyroiditis, immunoglobulin G4-related thyroid disease, PTC with nodular fasciitis-like stroma, mesenchymal neoplasms (e.g. solitary fibrous tumor, fibromatosis), or metastatic neoplasms with desmoplasia that may warrant ancillary tests to confirm their diagnosis. Although the presence of nuclear atypia, vascular invasion, and perineural invasion can be seen with paragangliomas these findings do not predict malignant behavior. Only focal nuclear pleomorphism was identified in some of our cases. Nevertheless, true malignancy for paragangliomas is defined by virtue of metastasis to a non-endocrine location, such as cervical lymph nodes, lungs, or liver.

In summary, although our cohort is limited to five cases, this series represents the largest collection to date characterizing the cytomorphology of thyroid paragangliomas with histopathologic correlation. In all cases, thyroid paragangliomas were misdiagnosed on FNA as follicular neoplasms, both due to the rarity of these tumors in this location and their cytomorphology mimicking follicular-patterned clusters without background colloid. The presence of naked nuclei, focal marked anisonucleosis, sustentacular cells, and absence of colloid are important cytologic clues that may help to triage FNA samples for ancillary testing to confirm the diagnosis.

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Case Number	Age/Gender	Clinical Presentation	Site	Size (cm)	Ultrasound Findings	Multicentric	Genetic test	Other Diagnoses
1	35/Female	Asymptomatic thyroid nodule	Left thyroid lobe	1.8	Hypoechoic, vascular nodule	No	None	Chronic lymphocytic thyroiditis
2	61/Female	Asymptomatic thyroid nodule	Left thyroid Lobe	3.0	Predominantly solid, hypoechoic, vascular nodule	No	SDHB mutation	Ovarian cancer, chronic lymphocytic thyroiditis
3	35/Female	Incidentally detected on CT scan	Left thyroid lobe	2.0	Hypoechoic, irregular, hypervascular nodule	No	None	Vagus nerve schwannoma, chronic lymphocytic thyroiditis
4	55/Female	Asymptomatic thyroid nodule	Isthmus and left lobe	3.0	Hypoechoic, vascular nodule	No	None	Micropapillary thyroid carcinoma, chronic lymphocytic thyroiditis
5	59/Female	Asymptomatic thyroid nodule	Right thyroid	3.0	Hypervascular, partially	No	None	Partially calcified porto-

TABLES

Table 1: Clinical, radiologic and genetic findings in this thyroid paraganglioma case series

			lobe		calcified, heterogeneous mass replacing much of the right lobe			caval mass

Table 2. Summary of cytology procedures, cytologic diagnoses and surgical resections

Case number	FNA passes	Slides prepared	ROSE diagnosis	Final cytology diagnosis	IHC on cytology material	FNA complications	Follow-up surgery	Frozen section diagnosis	Final histopathology diagnosis	IHC on resection	Operative complications
1	2	4 smears	None	Follicular neoplasm (Bethesda category IV)	None	None	Total thyroidectomy	None	Paraganglioma	Yes	None
2	5	10 smears and 1 LBC	Adequate	Follicular neoplasm (Bethesda category IV)	None	None	Total thyroidectomy	None	Sclerosing paraganglioma with positive margins	Yes	Left vocal cord paralysis
3	2	4 smears and 1 LBC	None	AUS/FLUS (Bethesda category III)	None	None	Left lobectomy	Follicular lesion	Sclerosing paraganglioma with positive margin	Yes	None
4	8	17 smears	Adequate	Follicular neoplasm (Bethesda category IV)	Non-contributory[a]	None	Left lobectomy	Cellular thyroid lesion, defer to permanent	Paraganglioma	Yes	None
5	3	4 smears and 1 LBC	Adequate	Suspicious for follicular neoplasm (Bethesda category IV)	None	None	Right lobectomy	Suspicious for medullary thyroid carcinoma	Paraganglioma	Yes	Excess blood loss, right vocal cord paralysis

a Thyroglobulin and calcitonin stains were performed on smears with non-contributory results

AUS/FLUS=atypia of undetermined significance or follicular lesion of undetermined significance

FNA=Fine needle aspiration

IHC=Immunohistochemistry

LBC=liquid based cytology

ROSE= rapid onsite evaluation

Table 3: Spectrum of cytoplasmic cytomorphologic findings in thyroid paragangliomas

Case number	Cellularity	Cell arrangement	Mimics follicles	Glandular features	Cell size	Cell shape	Cell cytoplasm	Cell granules	Cytoplasmic borders
1	Hypercellular	Small loose clusters, dispersed isolated cells	Yes	No	Medium	Round-oval	Abundant, clear to vacuolated	No	Distinct
2	Hypercellular	Small loose and tight clusters, dispersed isolated cells	Yes	No	Medium-large	Round-oval and spindle	Moderate, clear to eosinophilic to vacuolated	No	Indistinct to distinct
3	Hypocellular	Small loose and tight	Yes	No	Medium	Round-oval,	Moderate, eosinophili	No	Indistinct to distinct

		clusters, dispersed isolated cells				spindle and plasmacytoid	c		
4[b]	Hypocellular	Small loose clusters, dispersed isolated cells	Not available	Not available	Not available	Not available	Not available	Not available	Not available
5	Hypocellular	Small clusters, dispersed isolated cells	No	No	Medium	Oval and plasmacytoid	Moderate, eosinophilic	No	Indistinct

b Case 4 was an outside consult case and slides were unavailable for detailed repeat review

Table 4: Spectrum of nuclear cytomorphologic and background findings in thyroid paragangliomas

Case number[b]	**N:C rat**	**Nuclear atypi**	**Nuclear irregul**	**Intranuclear**	**Nucleoli**	**Naked nucl**	**MNG cell**	**Colloid**	**Melanin**	**Necrosis/**	**Background**	**Blood vessels**

	io	**a**	**arities**	**pseudoinclusions**		**ei**	**s**			**mitoses**		
1	Low	Yes	Yes	No	None	Few	Yes	None	No	No	Lymphocytes, monocytes	Yes, many
2	Low	Yes	Focal	Yes	Focal	Many	Yes	None	No	No	Possible sustentacular cells, lymphocytes, blood	Yes, many
3	Low	Yes	Focal	No	Focal	Few	Yes	None	No	No	Possible sustentacular cells, lymphocytes, blood	Yes
5	Low	Yes	No	No	None	Few	None	None	No	No	Blood	Yes

b Case 4 was an outside consult case and slides were unavailable for detailed repeat review

MNG=multinucleated giant cell

N/C= nuclear:cytoplasmic ratio

Table 5: Immunohistochemistry in the differential diagnosis of thyroid paragangliomas

Immunomarker	**Paraganglioma**	**MTC**	**Follicular lesion**	**HTT**	**PTC**
Cytokeratin	-	-	+/-	+	+ (CK-19)
Chromogranin A	+	+	-	+	-
Calcitonin	-	+	-	-	-
CEA	-	+	-	-	-
Galectin-3	-	+	-	-	+
HBME	-	-	-	-	+
Ki-67	variable	variable	variable	membranous	variable
Parathormone	-	-	-	-	-
Synaptophysin	+	+	-	-	-
S-100	+ (sustentacular cells only)	-	-	-	-
TTF-1/PAX-8	-	+ (weak)	+	+	+
Thyroglobulin	-	+	+	+	+

CEA= Carcino-embryonic antigen

CK=Cytokeratin

HBME= Hector Battifora MEsothelioma

HTT=Hyalinizing trabecular tumor

MTC= Medullary thyroid carcinoma

PTC= Papillary thyroid carcinoma

PAX= PAired Box

PTH= Parathyroid hormone

TTF= Thyroid transcription factor

FIGURE LEGENDS

Figure 1. FNA smear showing dispersed cells of medium to large size including scattered isolated plasmacytoid cells with moderate to abundant cytoplasm and round to oval nuclei showing anisonucleosis. Note the focal loose clusters of cells mimicking follicles (open arrow), occasional sustentacular cells (black arrows) with elongated nuclei, and several naked nuclei in the background (Diff Quik stain, Magnification 400x).

Figure 2. FNA showing loosely cohesive clusters of epithelioid cells with oval nuclei, focal conspicuous nucleoli and mildly irregular nuclear contours (Papanicolaou stain, Magnification x 400).

Figure 3. FNA smears showing epithelioid cells with (arrows) round to oval nuclei and intranuclear pseudo-inclusions (Diff Quik stain, Magnification 400x).

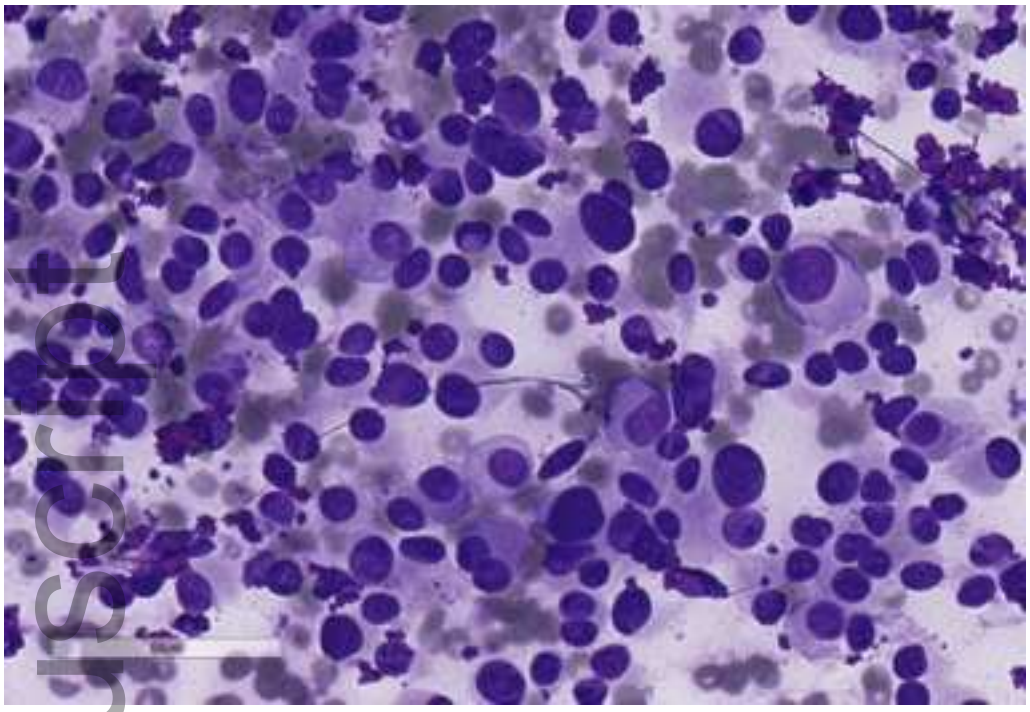
Figure 4. FNA smear showing several naked nuclei stripped of cytoplasm and marked anisonucleosis (Diff Quik stain, Magnification 400x).

Figure 5. Direct smear showing a transgressing blood vessel surrounded by plasmacytoid cells with amphophilic cytoplasm and indistinct cell borders (Diff Quik stain, Magnification 400x).

Figure 6. ThinPrep slide of a FNA sample obtained from a sclerosing paraganglioma showing a tight cohesive cluster of cells with mildly overlapping oval nuclei (Papanicolaou stain, Magnification x 400).

Figure 7. Resected paraganglioma morphology. **(A)** Nests of chief cells are shown arranged in an alveolar (Zellballen) pattern with a rich intervening capillary network (Hematoxylin and Eosin stain, Magnification x400). **(B)** Chief cells are positive for chromogranin A (Immunohistochemistry, Magnification x200). (**C)** Sustentacular cells are positive for S-100 protein (Immunohistochemistry, Magnification x200).

Figure 8. Resected sclerosing paraganglioma morphology. **(A)** Gross image of a sclerosing paraganglioma showing a tan-yellow poorly circumscribed nodule surrounded by brown to beefy red normal thyroid parenchyma. **(B)** Irregular cords of tumor cells surrounded by extensive sclerotic stroma simulating an invasive malignant neoplasm (Hematoxylin and Eosin stain, Magnification x4). **(C)** Tumor region showing typical nests of epithelioid tumor cells with clear to eosinophilic granular cytoplasm (Hematoxylin and Eosin stain, Magnification x400). **(D)** Tumor region showing scattered large hyperchromatic nuclei (Hematoxylin and Eosin stain, Magnification x200).



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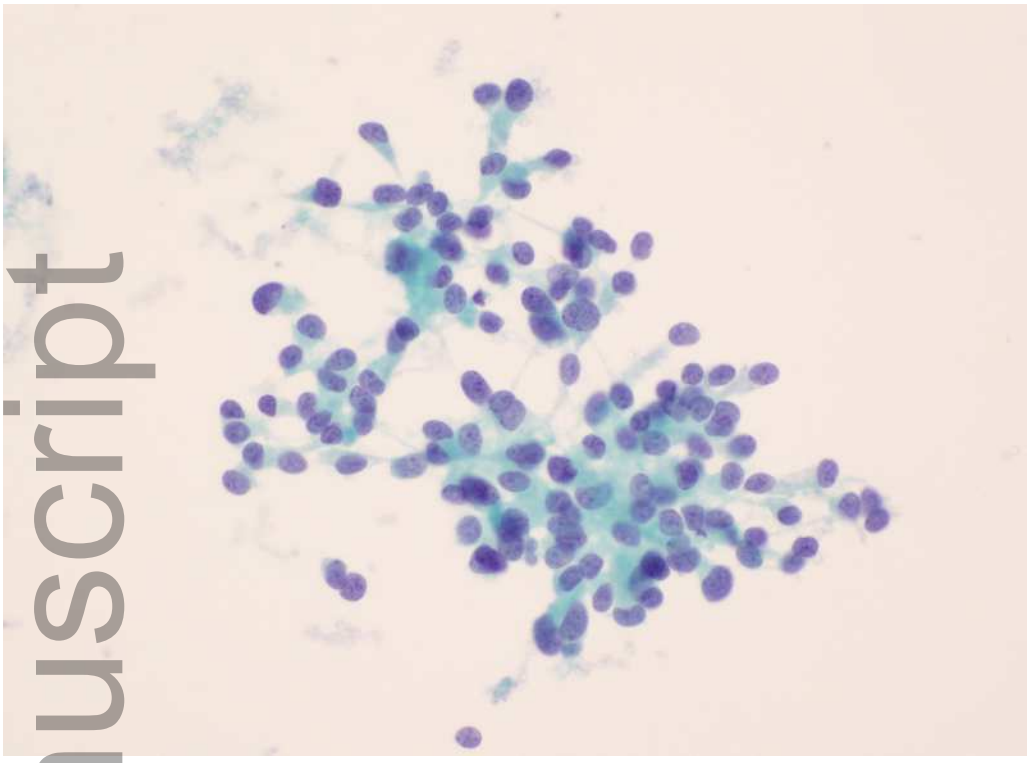

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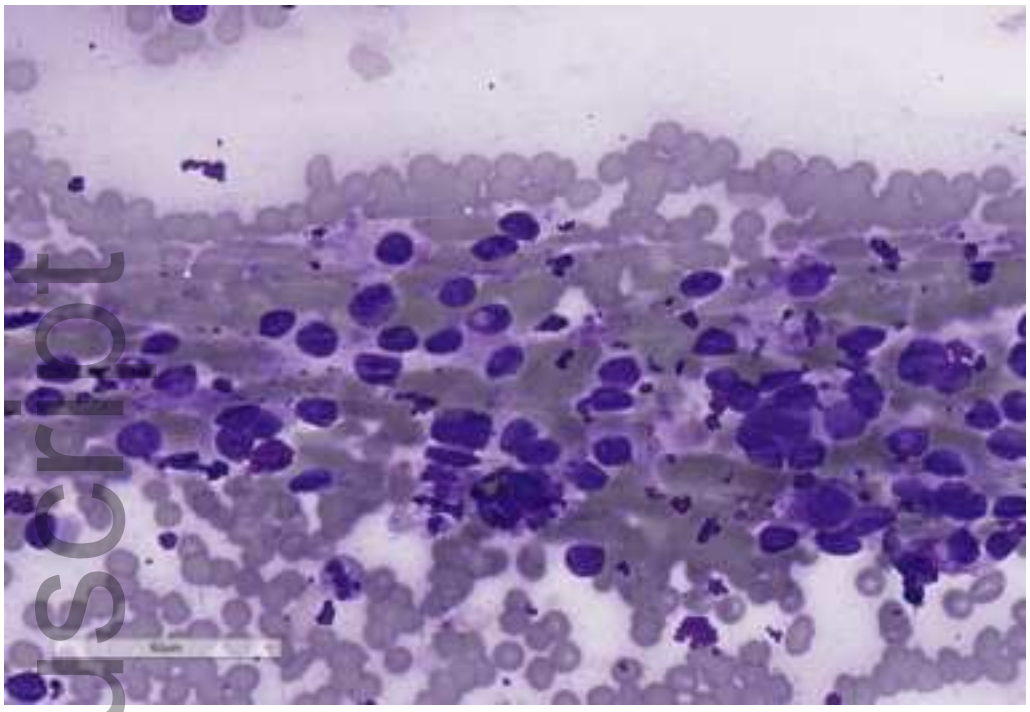

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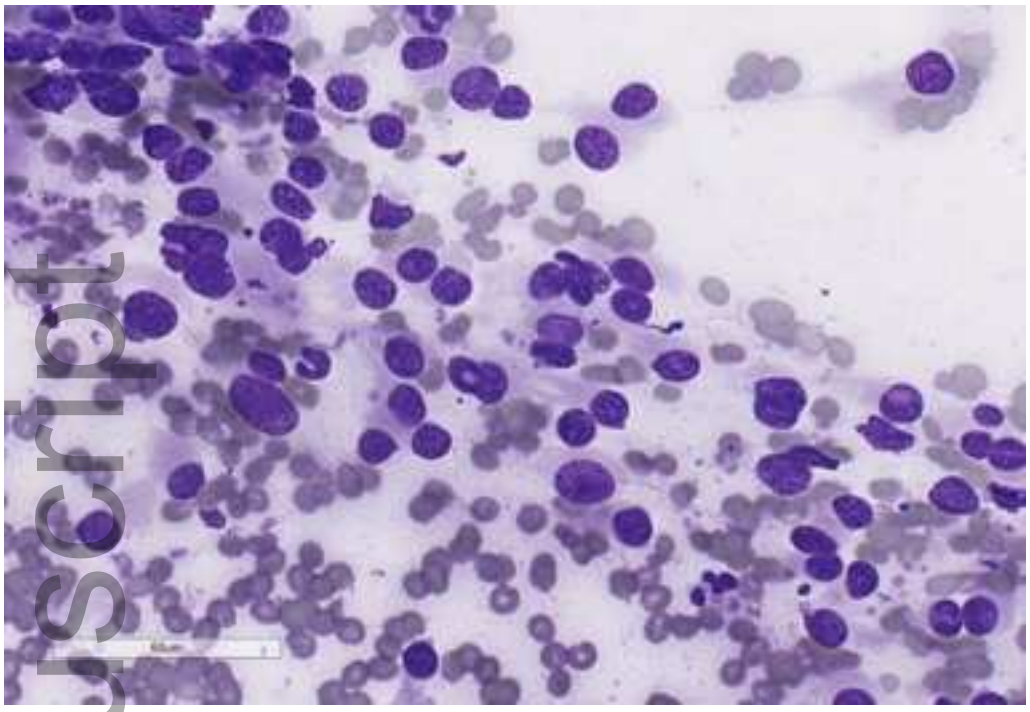

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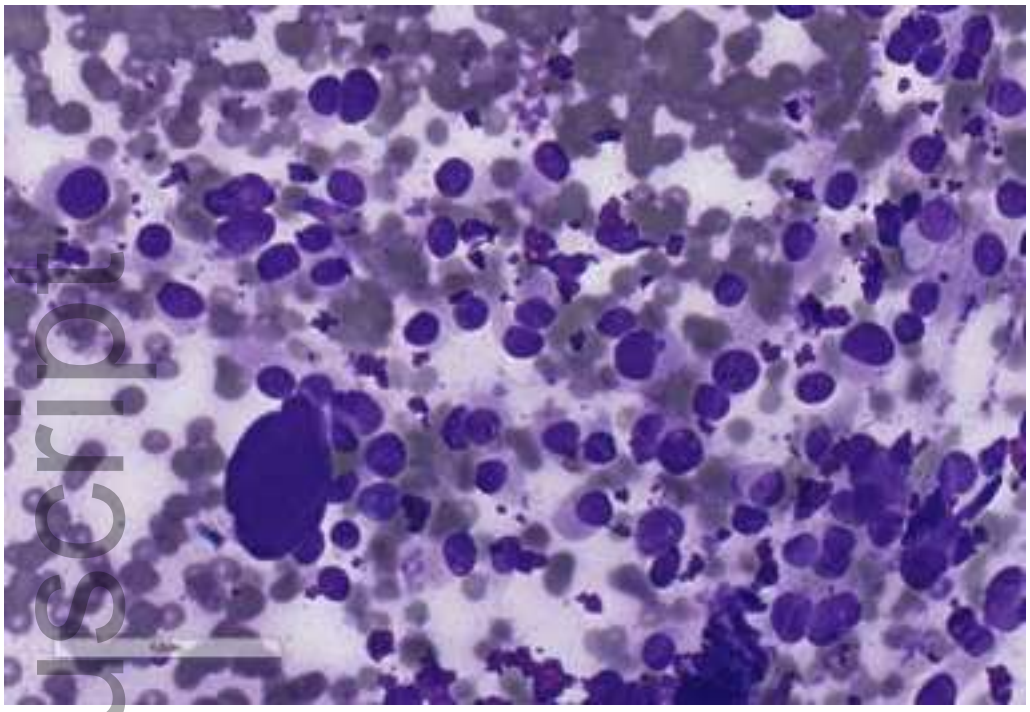

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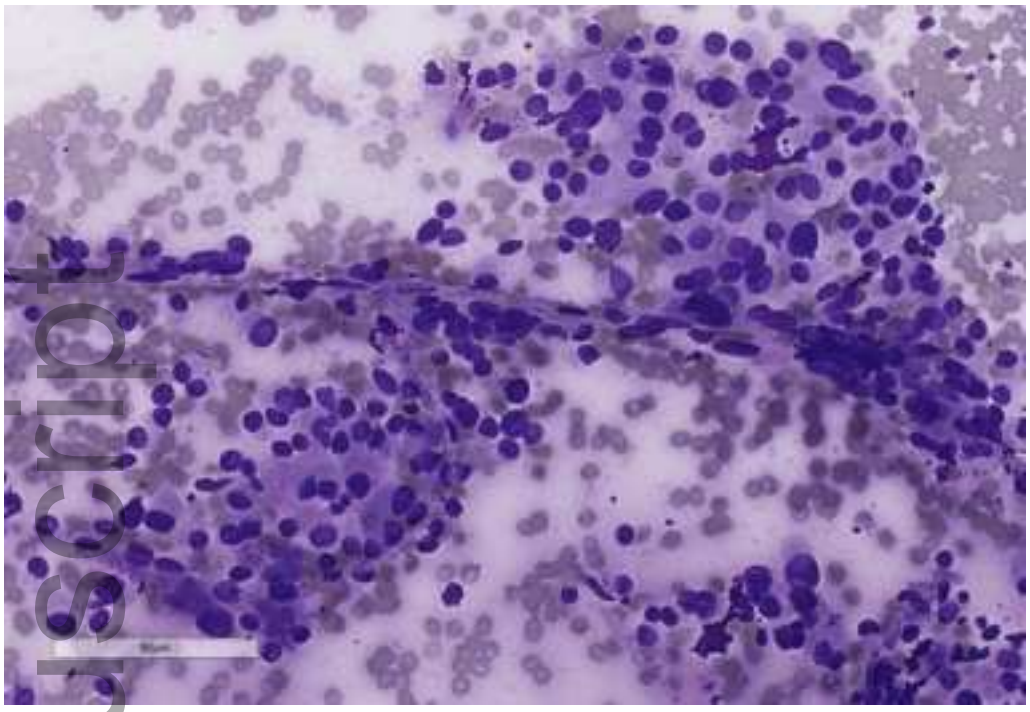

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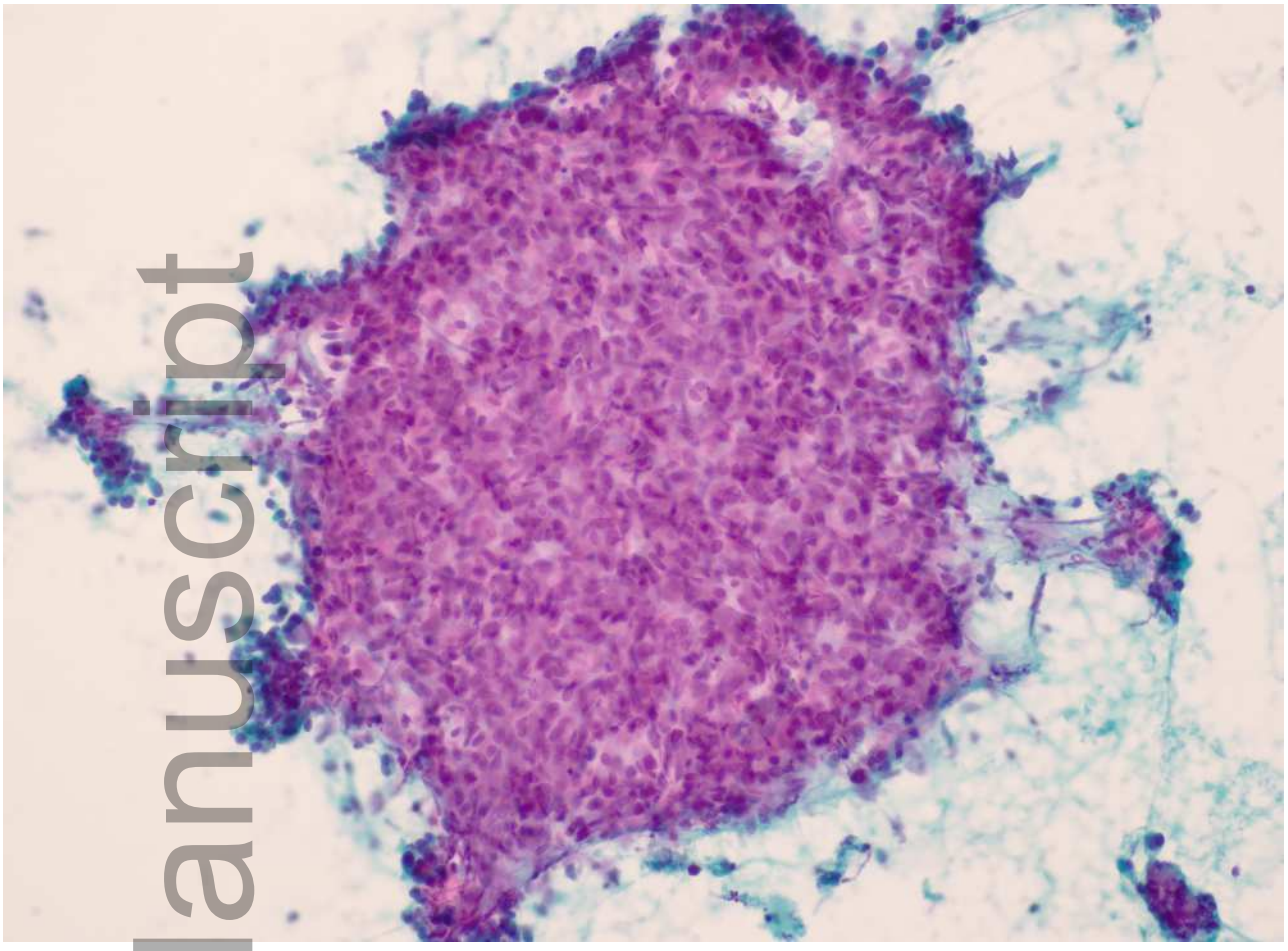

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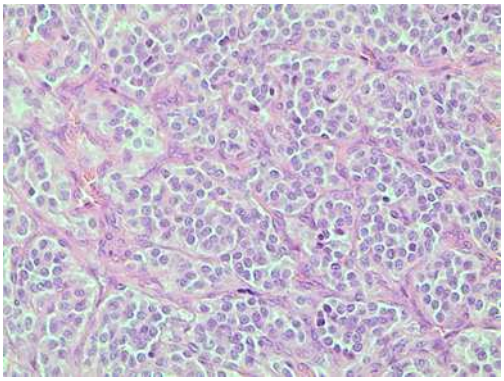

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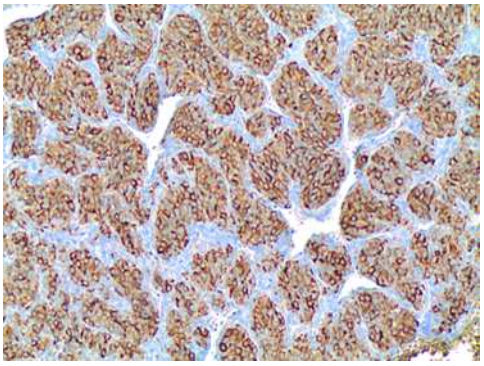

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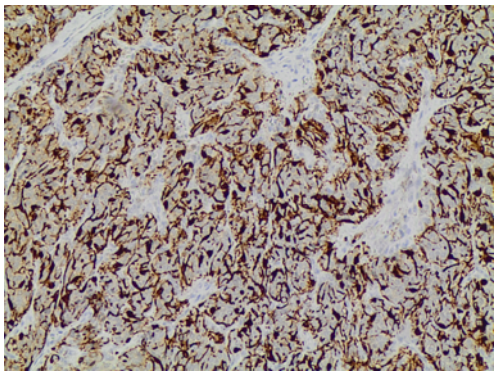

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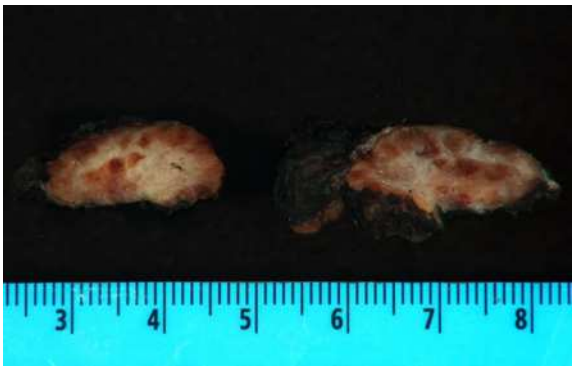

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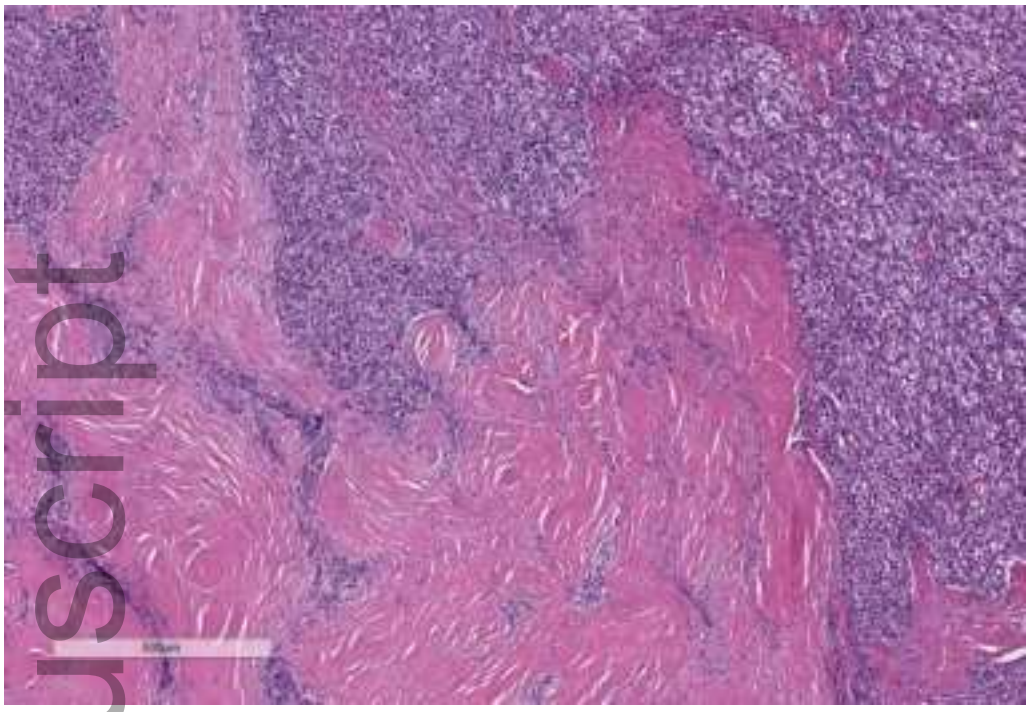

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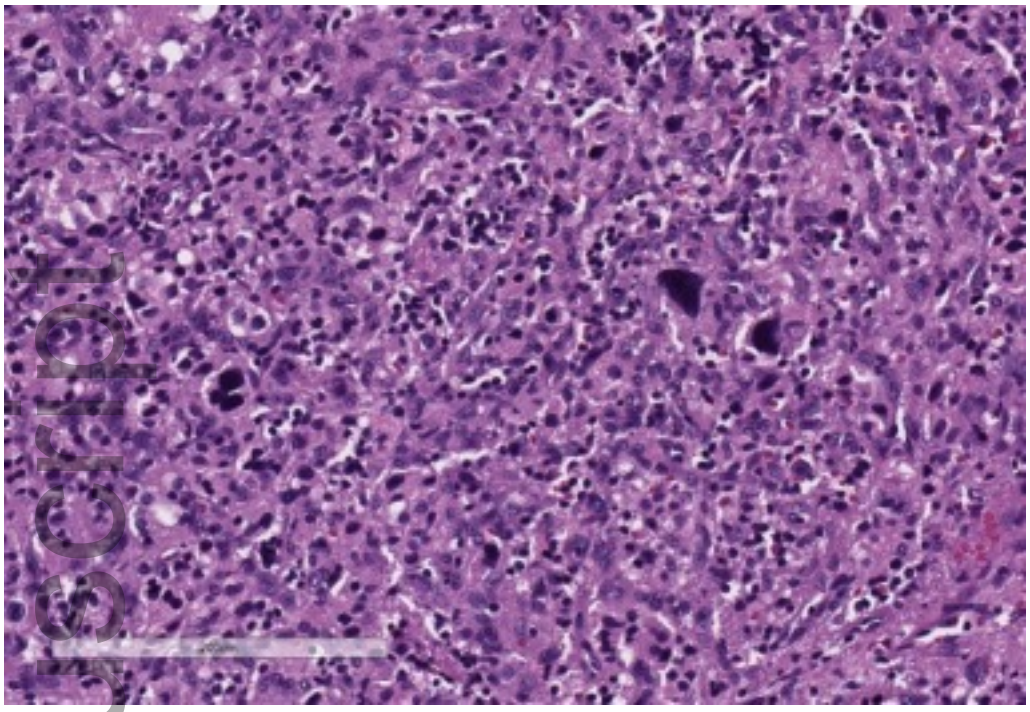

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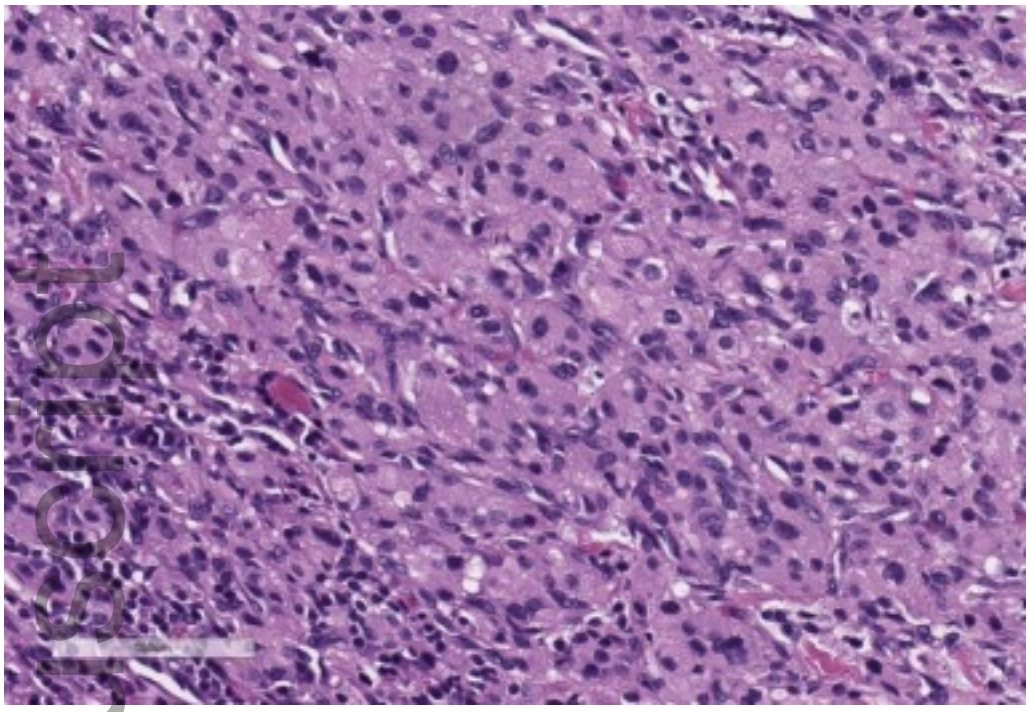

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