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Commentary

Pathogenesis and Morphology of Multifocal Thyroid Lesions

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DESCRIPTION

Multifocal thyroid lesions represent a complex and clinically significant subset of thyroid pathology characterized by the presence of multiple distinct nodules within the thyroid gland. These lesions encompass a wide spectrum of benign and malignant conditions, including multinodular goiter, follicular adenomas, papillary thyroid carcinomas, and medullary thyroid carcinomas. The development of multiple foci within a single gland reflects a combination of genetic, environmental, and epigenetic influences that disrupt normal thyroid architecture and cellular homeostasis. Understanding the pathogenesis and morphological features of multifocal thyroid lesions is critical for accurate diagnosis, prognostication, and surgical planning.

The pathogenesis of multifocal thyroid lesions is multifactorial, involving both intrinsic and extrinsic factors. Genetic predisposition plays a central role, particularly in the development of malignant foci. Papillary thyroid carcinoma, the most common thyroid malignancy associated with multifocality, frequently demonstrates activating mutations in genes involved in the mitogen-activated protein kinase signaling pathway, such as *BRAF* and *RAS*, as well as rearrangements involving *RET* and *NTRK* genes. These mutations drive uncontrolled cellular proliferation, survival, and differentiation, leading to the formation of multiple independent tumor foci. In contrast, benign lesions such as follicular adenomas often arise from localized clonal expansions without significant driver mutations, reflecting hyperplastic or proliferative processes rather than malignant transformation.

Epigenetic alterations and microenvironmental influences further contribute to the emergence of multifocal thyroid lesions. Chronic inflammation, autoimmune thyroiditis, and iodine deficiency create a permissive environment for lesion formation by inducing oxidative stress, cytokine release, and alterations in thyroid-stimulating hormone signaling. These factors may act in concert with genetic alterations to produce both synchronous and metachronous nodules, accounting for the diverse histopathological features observed within the gland.

Morphologically, multifocal thyroid lesions display considerable heterogeneity, reflecting the underlying pathogenesis. In benign multinodular goiter, nodules are typically well-circumscribed, varying in size from millimeters to several centimeters. The nodules often demonstrate hyperplastic follicular architecture with colloid accumulation, and the intervening thyroid parenchyma may exhibit atrophy or fibrosis. Follicular adenomas are usually solitary within each focus but may occur simultaneously in multiple locations, presenting as encapsulated lesions with uniform follicular structures and minimal cytological atypia. The presence of multiple adenomas highlights the propensity for clonal expansion within the thyroid and underscores the need for thorough pathological examination to differentiate benign nodules from malignant counterparts.

Malignant multifocal thyroid lesions, particularly papillary thyroid carcinoma, display characteristic nuclear features, including enlargement, overlapping, clearing, and grooves. Multifocality in papillary carcinoma may result from intraglandular metastasis or independent clonal events. Histological examination often reveals discrete tumor nodules separated by normal or hyperplastic thyroid tissue, with occasional evidence of lymphovascular invasion connecting foci. Some cases exhibit a mixture of classical and follicular variants within the same gland, reflecting divergent differentiation pathways. Medullary thyroid carcinoma, derived from parafollicular C cells, can also present as multifocal lesions, particularly in the context of hereditary syndromes such as multiple endocrine neoplasia type two. These foci demonstrate amyloid deposition, nested growth patterns, and neuroendocrine features, distinguishing them from follicular-derived lesions.

The architectural organization of multifocal lesions provides insights into their biological behavior. Benign nodules are generally well-circumscribed and encapsulated, whereas malignant foci may exhibit infiltrative borders, stromal desmoplasia, and perineural invasion. The presence of multifocality in thyroid carcinoma has been associated with a higher risk of lymph node metastasis and recurrence, although its impact on overall survival remains debated. Morphological assessment of surgical specimens is essential to guide the extent of thyroidectomy, determine the need for central neck dissection, and plan postoperative monitoring. Thorough sampling of all nodules, particularly in the context of suspicious

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features on imaging or fine-needle aspiration, is critical to avoid underdiagnosis and ensure complete resection of malignant foci.

Histopathological evaluation of multifocal thyroid lesions also involves assessment of the surrounding thyroid parenchyma. Background changes such as chronic lymphocytic thyroiditis, fibrosis, and vascular alterations may influence nodule development and mimic malignant infiltration. Differentiating independent tumor foci from intraglandular spread is essential, as it affects staging and therapeutic decision-making. Immunohistochemical markers, including thyroglobulin, calcitonin, galectin-3, and cytokeratin profiles, aid in distinguishing follicular-derived lesions from medullary or poorly differentiated carcinomas.

Clinical implications of multifocal thyroid lesions extend beyond pathology. Accurate identification of multifocal disease is critical for surgical planning, as subtotal thyroidectomy may leave residual malignant foci in situ, whereas total thyroidectomy provides a more definitive approach in patients with high-risk features. The risk of recurrence, the need for radioactive iodine therapy, and the intensity of postoperative surveillance are influenced by the number, size, and histological characteristics of the lesions. Furthermore, recognition of hereditary syndromes associated with multifocal thyroid disease, such as multiple endocrine neoplasia and familial adenomatous polyposis, has implications for genetic counseling and screening of at-risk family members.

CONCLUSION

Multifocal thyroid lesions encompass a diverse array of benign and malignant entities arising from complex interactions between genetic predisposition, environmental influences, and epigenetic regulation. Morphologically, these lesions exhibit heterogeneity in architecture, cellular differentiation, and growth patterns, reflecting underlying pathogenic mechanisms. Comprehensive evaluation, including careful histopathological examination, immunohistochemical profiling, and molecular analysis, is essential for accurate diagnosis, prognostication, and therapeutic planning. Recognition of multifocality has important clinical implications for surgical management, risk assessment, and postoperative follow-up.