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Clinical features, laboratory findings and histopathology of thyroid cancer: A literature review

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Abstract

Thyroid cancer is the most common malignancy of the endocrine system and represents a growing global health concern, particularly within the framework of non-communicable diseases. This literature review aims to synthesize current evidence regarding the clinical characteristics, thyroid hormone profiles, and histopathological classifications of thyroid cancer. A comprehensive review of relevant studies was conducted using peer-reviewed international and regional literature focusing on clinical manifestations, thyroid function tests including thyroid-stimulating hormone (TSH) and free thyroxine (fT4) and histopathological subtypes of thyroid malignancies. The reviewed literature consistently demonstrates that thyroid cancer predominantly affects women and commonly presents in middle-aged to older adults, with neck mass being the most frequent clinical manifestation. Most patients exhibit euthyroid status, although higher or upper-normal TSH levels are frequently associated with an increased risk of malignancy, while fT4 levels are generally within normal limits. Histopathologically, papillary thyroid carcinoma is the most prevalent subtype, followed by follicular, medullary, and anaplastic carcinomas. Early-stage disease is commonly identified in settings with improved diagnostic access. In conclusion, clinical features, thyroid hormone profiles, and histopathological findings play complementary roles in the diagnosis and risk stratification of thyroid cancer. Understanding these characteristics is essential for early detection, appropriate management, and improving patient outcomes, aligning with global efforts to strengthen health systems and cancer care.

Keywords: Cancer; Thyroid; TSHs; fT4; Histopathological

1. Introduction

Thyroid cancer is the abnormal growth of cells occurring in the thyroid gland, an endocrine organ located at the anterior aspect of the neck, just below the larynx, and shaped like a butterfly. Among endocrine glands, thyroid cancer is the most common malignant tumor. In Indonesia, thyroid cancer ranks ninth among the ten most frequently diagnosed cancers [1]. Thyroid-stimulating hormone (TSH) plays a role in thyroid cancer carcinogenesis by acting as a growth stimulus for tumor cells. Both elevated and high-normal TSH levels are considered in the diagnostic evaluation of thyroid cancer and in determining subsequent management strategies. Increased TSH levels have been associated with a higher risk of thyroid malignancy [2]. Similar to TSH, thyroxine (T4) levels may also be elevated in patients with thyroid cancer. Although most patients with thyroid cancer present with normal free thyroxine (fT4) levels, many exhibit values that are higher on average compared with those observed in benign thyroid nodules. An increased fT4-to-fT3 ratio suggests a tendency toward malignancy, as malignant thyroid nodules demonstrate a reduced capacity to

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convert fT4 to fT3 compared with benign nodules [3]. Based on histopathological classification, thyroid cancer is divided into four main types: papillary, follicular, medullary, and anaplastic carcinoma. Papillary thyroid carcinoma is the most prevalent subtype, accounting for nearly 85% of all thyroid cancers, followed by follicular carcinoma (approximately 11%), medullary carcinoma (3–5%), and anaplastic carcinoma (2–5%) [4]. The clinical manifestations of thyroid cancer commonly include a palpable mass in the anterior neck, cervical lymph node enlargement, hoarseness, dyspnea, difficulty swallowing or breathing, and throat pain [5].

2. Review Content

2.1. Clinical Features of Thyroid Cancer

The clinical symptoms of thyroid cancer include a palpable or visible anterior neck mass or nodule, hoarseness, dyspnea, cervical lymphadenopathy, difficulty swallowing, breathing difficulties, and throat pain. Thyroid nodules are suspected to be malignant when certain risk factors are present, including patient age younger than 20 years or older than 50 years, a history of childhood radiation exposure, dysphagia, dyspnea, voice changes, hard nodule consistency, solitary nodules, rapid nodule growth, cervical lymph node enlargement, and signs of distant metastasis. During medical history taking for thyroid evaluation, important aspects include patient age, sex, history of radiation exposure, family history of thyroid cancer, family history of multiple endocrine neoplasia type 2 (MEN-2), familial polyposis, and Cowden syndrome. Relevant clinical symptoms to be assessed include hoarseness, difficulty speaking with a normal voice, cervical lymph node enlargement, dyspnea, dysphagia, and throat pain [6]. Physical examination in thyroid cancer includes assessment of the thyroid gland, palpation of the neck particularly the lateral cervical regions to evaluate for lymphadenopathy, and laryngeal evaluation to assess vocal cord function. The presence of a hard, firm, or diffuse mass accompanied by clinical signs of extrathyroidal extension, such as fixation of the larynx or trachea, and evidence of clinical metastasis raises suspicion of malignancy [7].

2.2. Laboratory Findings of Thyroid Cancer

In thyroid cancer, thyroid function is generally normal or increased. Serum TSH is routinely measured as an initial evaluation of thyroid nodules, while other laboratory parameters that may be assessed include thyroglobulin, calcitonin, carcinoembryonic antigen (CEA), calcium, and metanephrines in serum or urine [8]. Thyroid-stimulating hormone (TSH) plays a role in thyroid carcinogenesis by acting as a growth stimulus for tumor cells. Elevated or high-normal TSH levels are associated with increased malignancy risk and are useful in thyroid cancer staging, diagnosis, and guiding subsequent management. [2]. A study by Boelaert et al. [9] reported that the lowest risk of malignancy is observed in patients with subclinical hyperthyroidism (TSH < 0.4 mIU/L, first quartile), whereas a higher incidence of thyroid cancer is reported in patients with subclinical hypothyroidism (TSH > 5.5 mIU/L, above the fourth quartile). Serum TSH is therefore considered a useful predictor of malignancy in thyroid nodules, with higher levels associated with an increased risk of thyroid cancer. Serum TSH levels have been found to be higher in differentiated thyroid cancer and in advanced stages (stages III and IV) compared with early stages (stages I and II) [9,10]. Sasson et al. [3] reported that although most patients with thyroid cancer have normal fT4 levels, the mean fT4 values are higher than those observed in benign thyroid nodules. An increased fT4/fT3 ratio indicates a tendency toward malignancy, reflecting the reduced ability of malignant thyroid nodules to convert fT4 to fT3 compared with benign nodules. Thyroglobulin is produced by both normal thyroid cells and well-differentiated thyroid cancer cells; however, it cannot reliably distinguish malignant from benign tumors during initial evaluation. Markedly elevated thyroglobulin levels are typically associated with metastatic thyroid cancer [8].

2.3. Histopathological Types of Thyroid Cancer

Among all thyroid cancer types, papillary thyroid carcinoma is the most common. It is a well-differentiated malignancy arising from follicular cells and typically metastasizes via the lymphatic system rather than the vascular route. Prognosis largely depends on patient age and disease stage, with early-stage disease associated with favorable long-term survival. Papillary thyroid carcinoma includes several histological variants, such as follicular variant, classic papillary, diffuse sclerosing, tall cell, and columnar cell types, with the follicular variant accounting for more than 50% of cases. Macroscopically, papillary thyroid carcinoma typically appears as an ill-defined mass with variable size, firm consistency, a granular surface, and a whitish color. Histologically, it is characterized by papillary structures, irregular nuclei with deep nuclear grooves, psammoma bodies, and cytoplasmic invaginations forming pseudoinclusions. Exposure to low-dose radiation is associated with the development of papillary thyroid carcinoma in approximately 85–90% of cases. This subtype is also observed in hereditary conditions such as Cowden syndrome, Gardner syndrome, and familial adenomatous polyposis. Follicular thyroid carcinoma is the second most common type of thyroid cancer after papillary carcinoma. It is a well-differentiated malignancy originating from follicular cells and tends to metastasize hematogenously, most commonly to the lungs and bones, particularly in advanced stages. The prognosis of follicular

thyroid carcinoma is generally less favorable than that of papillary carcinoma. Follicular thyroid carcinoma typically occurs in older patients compared with papillary carcinoma. Macroscopically, it presents as a solid tumor of variable size with a thick fibrous capsule and a brownish surface. Histologically, it is characterized by a well-circumscribed infiltrative pattern composed predominantly of relatively uniform cells arranged in follicular structures [11]. Medullary thyroid carcinoma accounts for approximately 3–5% of all thyroid cancers and originates from parafollicular (C) cells of the thyroid gland. It may occur sporadically as a solitary tumor but is frequently associated with familial syndromes. Medullary thyroid carcinoma is commonly accompanied by regional lymphadenopathy and elevated serum calcitonin levels, reflecting its origin from calcitonin-secreting C cells. Common sites of metastasis include the liver, bones, adrenal glands, and lungs. Most familial cases are associated with RET gene mutations detectable by blood testing. Consequently, serum calcitonin measurement is essential for diagnosis and postoperative follow-up. Histologically, medullary thyroid carcinoma is characterized by round, plasmacytoid, polygonal, or spindle-shaped cells arranged in nests, follicles, cords, or mixed architectural patterns [12]. Anaplastic thyroid carcinoma is a rare entity, accounting for approximately 1% of all thyroid cancers. Despite its low incidence, it carries a very poor prognosis due to its rapid growth, aggressive behavior, and early invasion of adjacent tissues. Anaplastic thyroid carcinoma is an undifferentiated malignancy and often arises from the progression of previously well-differentiated thyroid carcinomas [8].

3. Conclusion

This literature review highlights that thyroid cancer presents with diverse clinical manifestations, largely normal thyroid function, and distinct histopathological patterns that together play a crucial role in diagnosis and risk stratification. Evidence consistently indicates that clinical features, serum TSH and thyroid hormone profiles, and histopathological classification particularly the predominance of papillary thyroid carcinoma are interrelated and contribute to disease staging, prognosis, and management decisions. Elevated or high-normal TSH levels and altered fT4/fT3 ratios emerge as important predictors of malignancy, while histopathology remains the cornerstone for definitive diagnosis and therapeutic planning. By integrating clinical assessment, laboratory evaluation, and histopathological findings, this review supports a more comprehensive approach to early detection and personalized management of thyroid cancer. Such an approach can improve patient outcomes, strengthen cancer care systems, and guide future research toward optimizing diagnostic strategies and public health interventions for thyroid cancer

Compliance with ethical standards

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Disclosure of Conflict of Interest

No conflict of interest to be disclosed.

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