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THYROID CARCINOMA WITH INSULAR COMPONENT: REPORT OF THREE CASES WITH DIFFERENT CLINICAL PICTURES

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Insular carcinoma of the thyroid is situated morphologically and biologically in an intermediate position between the well-differentiated and undifferentiated tumors and presents a variable clinical course in a widely heterogeneous spectrum. The present cancer staging system (TNM) for thyroid cancer considers differentiated and undifferentiated tumors while ignoring this intermediate type, which is also called poorly differentiated tumor. In addition to the limited data on this rare disease, some poorly differentiated thyroid tumors contain differentiated cancer areas at various rates. These factors may cause difficulties in estimating disease aggressiveness and prognosis. To solve this problem, various microscopic and immunohistochemical parameters can be assessed. In this paper we describe 3 patients affected by thyroid carcinoma with an insular component, who presented different clinical pictures. When these cases were examined, the TNM system failed in stage grouping for poorly differentiated thyroid tumors. Case 1 and case 2 had similar clinical stages according to the TNM staging system for differentiated tumors, but had different prognoses. Case 3, with more limited disease, had the highest rate of poorly differentiated areas but the lowest Ki-67 proliferation index. In conclusion, it is difficult to make claims about the clinical behavior and prognosis of thyroid carcinoma with an insular component based on the 3 cases reported in this study, but it can be speculated that there is a gap in the TNM system with regard to the staging of insular thyroid carcinoma. In this situation the assessment of microscopic and immunohistochemical features of the tumor may help to predict disease aggressiveness and patient risk. However, it is clear that there is a need for large-scale studies evaluating the prognostic importance of histopathological and immunohistochemical features in determining risk groups.

Key words: carcinoma, insular, thyroid.

Introduction

Thyroid carcinomas are traditionally classified into well-differentiated (papillary and follicular) and undifferentiated (anaplastic) carcinomas. While well-differentiated thyroid cancers have a better prognosis, the undifferentiated type is one of the most aggressive tumors in the human body. In 1984, Carcangiu *et al.*[1] described a distinctive poorly differentiated type of thyroid tumors, situated morphologically and biologically in an intermediate position between the well-differentiated and undifferentiated tumors. Its microscopic features were formation of solid clusters (insulae) of uniform tumor cells of small size. Presence of mitotic activity, frequent necrotic foci, and capsular and vessel invasion were the other characteristic findings.

The exact incidence of insular carcinoma, which is also called poorly differentiated carcinoma, is unknown because the criteria for its diagnosis are not uniform among pathologists. According to the study by Lam *et al.*[2], in which strict histopathological criteria were used, its incidence was reported to be 3% of all primary thyroid carcinomas and the 10-year survival rate was reported to be 42%. On the other hand, because of its being rare there is a lack of data to estimate the prognosis of insular thyroid carcinoma. The clinical behavior of these tumors is variable and shows a widely heterogeneous spectrum between the well-differentiated and undifferentiated types, but it is usually characterized by invasion and early metastases to the regional lymph nodes and other organs. Although the topic is controversial, many believe that anaplastic carcinoma of the thyroid may represent the dedifferentiation of well-differentiated carcinoma and the poorly differentiated type is an intermediate form progressing from differentiated to undifferentiated cancer. However, the present cancer staging system (TNM) for thyroid cancer considers differentiated and undifferentiated tumors while ignoring this relatively new intermediate type. So it seems that there are some problems in predicting the prognosis of such cases. Assessment of their various microscopic and immunohistochemical features to identify parameters predictive of survival may help to obtain valuable information. In this paper we describe 3 patients who had different clinical pictures of thyroid carcinoma with an insular component and we summarize their histopathological and immunohistochemical features.

Case reports

Case 1

A 70-year-old woman presented with a mass on the left side of the neck, which had grown rapidly in the last 2 months. On physical examination we found a mass measuring 5 x 4.5 x 4.5 cm and multiple conglomerated lymph nodes on the same side. Thyroid hormone

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levels were within the normal limits and the thyroglobulin level was 46.7 ng/mL (range, 0.35-4.95 ng/mL). Tracheal deviation towards the right was seen on direct roentgenogram. Ultrasonography showed a solid nodule with a heterogeneous echo pattern, covering almost the entire lobe (measuring 5 cm in diameter); the nodule was scintigraphically hypoactive. Cytopathological examination by fine-needle aspiration revealed a papillary carcinoma. No gross extrathyroidal extension was found during the operation. Total thyroidectomy and modified unilateral neck dissection were performed. The patient was discharged on postoperative day 2 with mild hypocalcemic symptoms. By the end of the first postoperative month, recurrent disease with widespread gross and fixed lymph nodes in both submental regions had developed. The patient was included in a radiotherapy program but the tumor was radioresistant and she died 3 months after the operation.

Case 2

A 62-year-old man presented with a mass at the left side of the neck with a history of 1 year. In the last 2 months the mass has started to grow faster, and the patient had developed difficulty in breathing and hoarseness. On physical examination there was an immobile mass approximately 6 x 5 x 6 cm in diameter on the left thyroid lobe and multiple enlarged lymph nodes on both sides of the neck. The boundaries between the thyroid and the conglomerated lymph nodes were not clear. Thyroid function tests were normal. Ultrasonography and magnetic resonance imaging showed a mass measuring 6 cm in the left lobe, and conglomerated lymph nodes measuring 4.5 cm in largest diameter. Cytological examination by fine-needle aspiration was indicative of follicular carcinoma. The patient underwent total thyroidectomy and bilateral modified neck dissection including excision of the left internal jugular vein, which was embolized by tumor cells, and strap muscles with gross tumor invasion. After the operation temporary bilateral recurrent nerve palsy developed and the patient was reintubated and admitted to the intensive care unit for 2 days. He was discharged on the 11th day after the operation without any respiratory distress. The patient received 150 mCi radioiodine therapy after the operation and has been disease free for 24 months under thyroid hormone replacement therapy.

Case 3

A 69-year-old woman with a 15-year history of gross multinodular disease had undergone bilateral subtotal thyroidectomy in another hospital 6 months previously. Pathological examination had reported a medullary carcinoma measuring 3.5 cm in size. Eight months after the primary surgery the patient, who did not want to be reoperated at the time, was referred to our center for reoperation. Histopathology slides and paraffin blocks of the former operation, which were reexamined in our pathology department, proved to be calcitonin negative and there was no amyloid accumulation. The microscopic diagnosis was insular carcinoma of the thyroid. There was no palpable mass on physical examination of the neck. The patient was in euthyroid state. Ultrasonography, scintigraphy and computed tomography showed bilateral thyroid remnants, but there were no thyroid nodules or involved lymph nodes. The patient underwent completion thyroidectomy and prophylactic central lymph node dissection. Histopathological examination of the specimen confirmed normal thyroid tissue and lymph nodes. The patient received 200 mCi radioiodine therapy. She has been under suppressive thyroid hormone therapy and disease free for 12 months from the initial operation.

Macroscopic and microscopic features

While case 1 had microscopic extrathyroidal extension, case 2 had gross invasion of the neighboring organs and a tumoral thrombus in the internal jugular vein. Hematoxylin and eosin-stained slides of the cases were reviewed. The tumors were characterized by tumor cells forming nests surrounded by hyaline stroma and composed of round or spindle cells with eosinophilic cytoplasm. Nuclear vesiculation and prominent nuclei were the dominant features of the tumor cells (Figure 1A, 1B, 1C). Mitotic activity was determined by counting the number of mitoses per 10 high power fields. Thyroglobulin was positive and calcitonin was negative in all tumors. There was no vascular or neural invasion in patient 1, who had a poorer prognosis. Necrosis was widespread in cases 1 and 2 and focal in case 3. No tumor was purely insular. The associated tumoral components of the insular lesions in case 1, 2, and 3 were papillary, follicular and oncocytic, respectively. The microscopic features of the tumors are presented in Table 1.

Immunohistochemical features

Samples were obtained from formalin-fixed, paraffin-embedded archival tissue blocks and immunostaining was performed using antibodies against Ki-67 (dilution 1:500; Neomarkers, Fremont, CA, USA) and p53 (dilution 1:50; Neomarkers). The number of stained cells per 1000 tumor cells was counted 2 times by the same pathologist using a standard light microscope and the mean numbers were given. Areas with the highest Ki-67 expression were considered for counting, and the results were expressed as percent of positive cells. While case 1 had the highest Ki-67 staining rate, case 3 had the lowest rate (Table 1). When the Ki-67 rates of the differentiated components were compared, case 1 also had the highest rate (Figure 1D, 1E, 1F). Evaluation of immunohistochemical staining for p53 was done solely on the basis of nuclear staining. The extent of staining was graded semiquantitatively using a – through 3+ scale, with – representing no staining at all, 1+ representing <25% staining, 2+ rep-

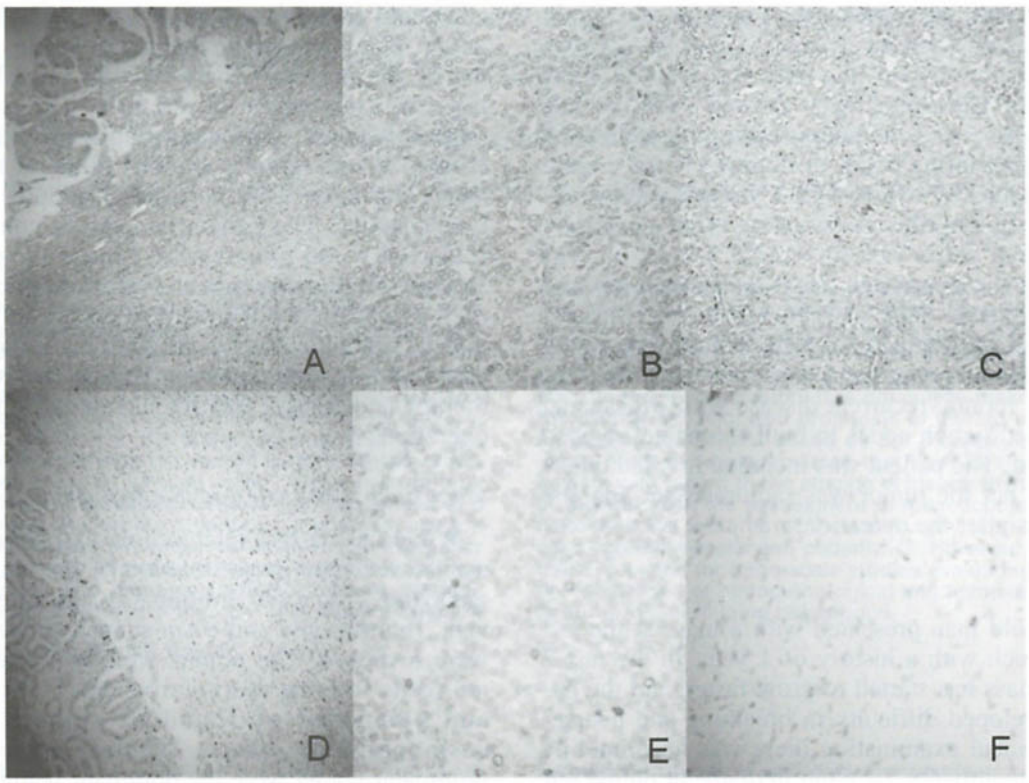

Figure 1 - A) Case 1 - Poorly differentiated and papillary carcinoma (top) patterns together, HE x100. B) Poorly differentiated area in case 2, HE x200. C) Spindle cell pattern in case 3, HE x200. D) Ki-67 expression in case 1, HE x100. E) and F) Ki-67 expression in cases 2 and 3, respectively, x200.

resenting 25-75% staining, and 3+ representing >75% staining of tumor cells present in the sections. According to this scale case 2 was negative, while cases 1 and 3 showed similar expression rates.

Table 1 - Clinical, microscopic and immunohistopathological features of the cases

Features	Case 1	Case 2	Case 3
Clinical features			
Age (years)	70	62	69
Tumor diameter (cm)	5	6	3.5
Metastatic lymph nodes	+ (ipsilateral)	+ (bilateral)	-
Distant metastasis	-	-	-
Muscle invasion	-	+	-
TNM stage (according to differentiated types)	T3N1bM0	T3N1bM0	T2N0M0
Microscopic features			
Poorly differentiated area (%)	30-40	50-60	80-90
Morphology of differentiated area	Papillary	Follicular	Oncocytic
Vascular invasion	-	+	+
Neural invasion	-	-	-
Necrosis	+	+	+
Mitotic activity	4	2	2
Immunohistopathological features Ki-67 rate in each component (%)			
Insular	35	7	4
Associated component	15	7	4
p53	++	-	++
Outcome	Died	Disease free	Disease free

Discussion

Insular carcinoma of the thyroid is situated morphologically and biologically in an intermediate position between the well-differentiated and undifferentiated tumor types and presents a variable clinical course in a widely heterogeneous spectrum[2-5]. Chao *et al.*[6] reported that the cumulative rates of lymph node metastases and distant metastases ranged between 50% and 84% and between 36% and 84%, respectively. The disease-specific mortality was between 9% and 75%. These wide ranges indicate that the relations between the clinical risk factors and the prognosis of patients with poorly differentiated cancer are not clear. On the other hand, because of the rarity of these tumors, the data accumulated about the behavior and prognosis of the disease is not sufficient. In addition, the present cancer staging system (TNM) for thyroid cancer considers differentiated and undifferentiated tumors while ignoring this intermediate type. Because of these problems, the estimation of patient risk is usually difficult in cases of insular carcinoma. In this situation the assessment of various histopathological and immunohistochemical parameters can be used to achieve valuable information about the aggressiveness of the disease. It is not possible to draw a conclusion on prognosis from the present study in-

cluding only 3 cases with short follow-up, but some of the data obtained may be helpful for a better understanding of this tumor type.

Patient age, status of the primary tumor, lymph nodes and presence of distant metastasis are common clinical predictors in evaluating patient risk for many tumors and these risks have also been well recognized for differentiated thyroid tumors. The same parameters may be valid for insular cancer; however, the data about their prognostic significance is not sufficient for this rare type of cancer with a widely varying clinical behavior. Moreover, the present TNM system published by the American Joint Committee on Cancer for clinical staging of thyroid carcinoma does not include poorly differentiated carcinoma, but considers only differentiated types and anaplastic carcinoma. These problems cause difficulties in determining clinical stage and predicting the prognosis of such cases. Advanced age can be considered a risk factor[3], but the cases presented here occurred in a similar age group and none of the 3 patients had distant metastasis. On the other hand, tumor size was similar in case 1 and 2, but case 3 had a smaller sized tumor. This can explain why patient 3 had a good prognosis, but not why patient 1 died and patient 2 was disease free. In addition, case 2 presented gross tumoral invasion to the neighboring organs and vessels and had bilateral lymph node metastases, but a better prognosis than case 1. These clinical parameters did not help us place our patients adequately in this wide clinical spectrum.

Well-differentiated (follicular or papillary), anaplastic and poorly differentiated components can be found together in a thyroid neoplasm[7]. There is controversy on whether insular carcinoma associated with well-differentiated histological components and their proportions in the tumor have an effect upon prognosis. Some authors argue that the relative proportion of well-differentiated and poorly differentiated components does not affect prognosis. In other words, there is no correlation between the extent of insular carcinoma and prognosis[3,8]. In fact, these proportions may be used more to explain the histogenesis of the tumor[7]. For instance, concomitant well-differentiated thyroid carcinomas were noted in both anaplastic and insular carcinomas; furthermore, anaplastic carcinomas may contain foci of insular carcinoma. These findings support the hypothesis that well-differentiated carcinoma can progress to the insular type and then to anaplastic carcinoma by dedifferentiation[2]. On the other hand, it was reported that an insular component by itself usually entails an unfavorable prognosis, irrespective of the extent of this component[3-5,9]. In our study, despite greater rates of poorly differentiated areas in cases 2 and 3, both cases had a better prognosis than case 1. The features of the insular components in the present cases were similar to the data mentioned above, but this information is insufficient to stratify patients into distinct groups with different risks.

It was reported that histological features based on a combined examination of nuclear atypia, tumor necrosis, and vascular invasion have prognostic significance in differentiated papillary thyroid carcinomas[10], but the value of histological grading in poorly differentiated tumors is not clear. Volante *et al.*[3] found that age >45 years, presence of necrosis and a mitotic count >3 are significantly important risk factors to recognize the clinically aggressive tumor with an insular component and have suggested a scoring system using these clinicopathological parameters to define subgroubs with or without a high risk. When our 3 patients were evaluated according to these 3 criteria, all patients were over the age of 45 and had necrosis. Mitotic count was above 3 in case 1 having the worst prognosis, but the mitotic counts were the same in the other 2 patients who had different clinical pictures. These criteria can be useful to estimate the behavior of the disease, but may need to be developed further for an adequate determination of risk groups.

Immunohistochemical examination of molecular features can provide more valuable information for a better assessment of cancer aggressiveness. Measurement of cell cycle kinetics by immunohistochemical methods can provide some benefits for predicting prognosis. Ki-67, which is a nuclear antigen expressed by cells in the proliferative phases, is employed as a cell proliferation marker and monoclonal antibodies are used to detect its expression. A high rate of Ki-67 expression indicates high mitotic activity in a tumor. However, the clinical significance of Ki-67 expression in specimens of thyroid cancers with an insular component has not been fully investigated. It was reported that the Ki-67 labeling index was well correlated with differentiation of thyroid carcinoma[7,11]; this finding supported the classification of these carcinomas into prognostically relevant categories as differentiated, poorly differentiated and undifferentiated[11]. It was also shown that Ki-67 index as a prognostic tool was helpful in estimating the median survival of individual patients with medullary thyroid cancer[12]. Additionally, Tallini *et al.*[11] showed that a high proliferation rate was associated with poor survival and morbidity. In our study, case 1, with the poorest prognosis, had the highest Ki-67 expression, case 2, with a better prognosis but advanced disease, had a lower Ki-67 rate, and case 3, with limited disease, had the lowest proliferation rate. These findings are in concordance with the information above, and we may thus explain why our patients presented different clinical pictures. If the Ki-67 proliferation index is useful in predicting patient morbidity and mortality, it may also be useful to categorize patients with an insular component into subgroups for predicting their risk and prognosis more accurately. But the data on this issue are limited.

Overexpression of p53 has been found as a possible prognostic factor in thyroid carcinoma[13]. It was reported that the mutation rate of the p53 gene in thyroid carcinoma with an insular component was 38% and this association might play an important role in the behavior of thyroid carcinoma[14]. In another study[2], while increased p53 expression was found in 69% of anaplastic thyroid carcinomas, it was found in only 3% of insular

cancer. Additionally, it was reported that p53 expression might be an indicator of dedifferentiation from insular carcinoma to anaplastic cancer[2], but it is not clear whether the expression rate can be used as a risk factor in recognizing risk subgroups among patients having thyroid carcinoma with an insular component. In our patients, case 2 with advanced disease did not show p53 expression, but cases 1 and 3 did.

In conclusion, it is difficult to make any claims about the clinical behavior and prognosis of thyroid carcinoma with an insular component based on the 3 cases reported in this study, but it is clear that there is no consensus favoring any of the prognostic indices for predicting disease behavior. At this point, the assessment of some microscopic and immunohistochemical features in addition to the clinical findings may help to predict disease aggressiveness, and to stratify patients into distinct groups with different risks. However, the currently available data on this issue are limited and there is a need for new and large-scale studies evaluating the prognostic importance of clinicopathological parameters in such cases.

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