Insular carcinoma was described some thirty years ago as a distinctive type of thyroid carcinoma, characterized by the formation of solid masses or islands (insulae) of small monomorphic tumor cells with aggressive clinical behavior, distant metastases, and death in most instances. The authors believed that this carcinoma occupies a place intermediate between well-differentiated follicular/papillary carcinomas and the usually fatal anaplastic carcinoma. They referred to this morphologic type as poorly differentiated carcinoma and coined the term “insular” because of the characteristic histologic appearance. In 2006, a consensus conference in Turin, Italy, proposed a definition of poorly differentiated thyroid carcinoma (PDTC): The lesions are of follicular cell origin, composed of nests, insulae, or trabeculae of tumor cells that appear primitive, with scant cytoplasm and a high nuclear-to-cytoplasmic ratio; there is tumor necrosis, mitoses easily identified, lymphovascular invasion, and involvement of surrounding parenchyma and extrathyroidal soft tissues.

Insular carcinomas are uncommon, comprising 4% to 7% of all thyroid malignancies with a male:female ratio of 1:2. Insular carcinoma usually occurs in older individuals, the mean age being 55 years. But it has also been described in the pediatric age group and adolescents. These tumors follow an aggressive course with a high mortality rate. Most patients demonstrate local and distant metastases at the time of presentation.

GROSS AND HISTOLOGIC FINDINGS
Grossly, insular carcinomas are usually large, bulky, often exceeding 5 cm in dimension. They are solid, grayish white with foci of necrosis (Fig. 10.1). Gross extrathyroidal extension is frequently present.

Insular carcinomas demonstrate distinctive histologic appearance (Figs. 10.2 to 10.4), characterized by a solid growth pattern consisting of well-defined nests or insulae of round-to-oval, small follicular cells averaging up to 10 μm in diameter. The nuclei are described as convoluted, and the nuclear membranes are irregular and deeply-stained, appearing raisinoid, with occasional grooves and no intranuclear inclusions.

The nests of the tumor cells are well demarcated; vary in size, separated by thin connective tissue septae containing delicate blood vessels. The nests of tumor cells may be solid, or show a follicular pattern, often with abortive follicles or a trabecular pattern. Large areas of necrosis are frequent (Fig. 10.4). Sparing of malignant cells around the blood vessels imparts a peritheliomatous pattern. Mitoses are frequent. Droplets of colloid may be present in the abortive follicles. Insular carcinomas may be associated with well-differentiated follicular/papillary carcinomas, or anaplastic carcinomas. Macrofollicular variant of papillary carcinoma has been particularly described to be associated with an insular component.

Insular pattern is also observed in metastases from differentiated follicular/papillary carcinomas (see Fig. 10.10).

CYTOPATHOLOGIC FEATURES
The cytopathologic findings of insular carcinomas are sparsely documented. Their presentation varies, the common denominator being the consistent small cell size. The aspirates are generally cellular, consisting of a large population of small, very uniform malignant cells occurring singly, in loosely cohesive groups, and in syncytial tissue fragments (Figs. 10.5 to 10.12). The latter occur as nests, masses, or trabeculae with intense crowding and overlapping of nuclei. The nests are often rounded and sharply defined, corresponding to the insulae seen in the histologic sections. Some syncytial tissue fragments may demonstrate a microfollicular pattern with their lumens at times containing droplets of colloid (Fig. 10.10C). A dispersed pattern is also occasionally seen (Fig. 10.7). The cells of the insular carcinoma are round, with poorly defined cell borders, and are much smaller than those of the differentiated (follicular/papillary) thyroid cancers, averaging 9 to 10 μm in diameter. Plasmacytoid features causing difficulties in differentiating the tumor from medullary carcinoma have been described. Their cytoplasm is scant, indiscernible, occasionally pale, and...
FIGURE 10.2. A. Histologic section of an insular carcinoma with a solid growth pattern and prominent vascularization (low power). B. Higher magnification showing small uniform malignant cells with scant cytoplasm and hyperchromatic nuclei.

FIGURE 10.3. A. Note a solid growth pattern with large islands of uniform malignant cells (insulae), delineated by delicate fibrous septae (low power). B. Higher magnification highlighting the small uniform malignant cells. Note the abortive follicles (arrows).

FIGURE 10.4. A. Histologic section of insular carcinoma showing a solid growth pattern with large areas of necrosis (low power). B. Higher magnification highlighting the small monotonous cells and abortive follicles (arrow), some containing colloid. C. Positive reactivity of the insular carcinoma cells to thyroglobulin.
vacuolated with extremely high N/C ratios. The nuclear contours are smooth, and the chromatin is coarsely granular, deep-staining. Excessive parachromatin clearing is also appreciated, and micronucleoli are usually conspicuous. Insular carcinomas dedifferentiated from papillary carcinomas may demonstrate features of papillary carcinoma such as powdery chromatin, nuclear grooves, and intranuclear inclusions. Those dedifferentiated from follicular carcinomas may demonstrate a follicular pattern. As mentioned in histologic findings, a metastatic carcinoma from a differentiated thyroid cancer may present as an insular carcinoma (Figs. 10.10 and 10.11). The background may be clean or necrotic. Mitosis may be a prominent feature. No colloid is appreciated in the background. The cytologic features of insular carcinoma are listed in Table 10.1 and illustrated in Figures 10.5 to 10.12.

IMMUNOPROFILE

The insular carcinoma cells usually react positively to thyroglobulin and TTF-1. Negative reactivity to thyroglobulin is occasionally observed. Insular carcinomas also react positively to cytokeratins.
FIGURE 10.6.  A, B. FNA of an insular carcinoma showing large syncytial tissue fragments of small, uniform malignant cells with extreme crowding and overlapping. Note a vague follicular pattern (arrows). “Insular” nature may not be recognized from the cytologic samples, and the carcinoma may be interpreted as poorly differentiated follicular carcinoma. C. Histologic section of the resected insular carcinoma.

FIGURE 10.7.  A, FNA of another case of an insular carcinoma. The cellular aspirate consists of small malignant cells, in syncytial tissue fragments with a follicular pattern. Note the dispersed pattern (low power). B. Higher magnification showing small, uniform malignant cells with scant cytoplasm, high N/C ratios, and granular chromatin with micronucleoli. Note the clean background. C. Histologic section of the insular carcinoma.
THYROID CYTOPATHOLOGY

DIAGNOSTIC ACCURACY AND DIFFERENTIAL DIAGNOSIS

The diagnostic accuracy of insular carcinoma is difficult to assess. These are uncommon thyroid neoplasms, and since first described over three decades ago, in 1984, cytologic findings of insular carcinoma are described only infrequently, usually as individual case reports or as small case series. In most of these reports, the cases were interpreted as poorly differentiated carcinomas, and the insular nature was appreciated following the histologic examination. An accurate cytologic diagnosis of insular carcinoma is difficult to make, unless the aspirate shows insulae formed by small uniform malignant cells. Most cases of insular carcinomas are cytologically interpreted as poorly differentiated follicular carcinomas because of the follicular architecture, or as papillary carcinomas if features of papillary carcinoma are coexistent. The presence of insulae is not a very common feature. Their recognition also depends on the experience of the

FIGURE 10.8. FNA of an insular carcinoma metastatic to the vertebra. Note the characteristic insula formed by small, uniform cells. There is an attempt at follicular growth pattern.

FIGURE 10.9. A. FNA of an insular carcinoma metastatic to the lung. Note syncytial tissue fragments forming insulae with well-defined outlines (low power). B. Higher magnification demonstrating monomorphic small follicular cells with high N/C ratios, presenting a follicular pattern.

FIGURE 10.10. This case represents a macrofollicular papillary carcinoma, which metastasized four years later to the shoulder with dedifferentiation. FNA of the shoulder mass showed an insular carcinoma that was confirmed on surgical excision. A. Histologic section of the macrofollicular papillary carcinoma. Note large follicles distended with colloid. The lining epithelium demonstrates classic nuclear features of a conventional papillary carcinoma. B. Higher magnification to highlight the classic nuclear features of a conventional papillary carcinoma. C. FNA of the shoulder mass showing small, uniform malignant follicular cells. Note occasional follicle formation and colloid in their lumens. D. Positive reactivity of the malignant cells to thyroglobulin. E. Histologic section of the excised shoulder mass showing insular carcinoma.
FIGURE 10.11. This case represents a follicular carcinoma that metastasized, eleven years later, to the lung as an insular carcinoma.

A. FNA of the follicular carcinoma performed preoperatively. Note syncytial tissue fragments with a follicular pattern. The component cells have intensely hyperchromatic, enlarged nuclei. B. The thyroidectomy revealed a very large fleshy tumor replacing the entire right lobe. C. Histologic section showed a widely invasive follicular carcinoma. Note vascular invasion (arrow). D. Higher magnification of the follicular carcinoma. E, F. FNA of the pulmonary metastasis showing a characteristic cytologic pattern of insular carcinoma with a follicular pattern. Compare the cell size in this metastatic tumor with the original tumor, as depicted in Figure 10.10A.
such as the follicular or papillary type. The aspiration biopsy may sample only the differentiated component, and the diagnosis of insular carcinoma will be evident only after the surgical excision. On rare occasions, however, multiple sampling of the neoplasm may demonstrate the coexistence of both components (Fig. 10.12).

interpreter, as most cytopathologists have limited experience with the cytologic presentation of this uncommon thyroid neoplasm. The small size of the malignant cells, however, is the key to the diagnosis. The conventional follicular carcinoma cells are much larger (Fig. 10.11A). Also, many insular carcinomas are associated with differentiated carcinomas of follicular cell origin such as the follicular or papillary type. The aspiration biopsy may sample only the differentiated component, and the diagnosis of insular carcinoma will be evident only after the surgical excision. On rare occasions, however, multiple sampling of the neoplasm may demonstrate the coexistence of both components (Fig. 10.12).
Chapter 10  POORLY DIFFERENTIATED (INSULAR) CARCINOMA

251

will be extremely difficult to differentiate from either a medul-
lar carcinoma or a metastatic small cell carcinoma. An example
is illustrated in Figure 10.15.

**Insular Carcinoma versus Malignant Non-Hodgkin Lymphoma**

A dispersed pattern of small malignant cells in an insular carci-
noma of the thyroid may be misinterpreted as malignant lym-
phoma (Figs. 10.16 and 10.17). Nuclear molding and stretch
artifacts are not present in either of the two malignancies. The
presence of increased proliferative activity, frequent mitotic fig-
ures, and necrotic background are features common to both.
Without immunostains such as thyroglobulin and lymphoid
markers, their differentiation may be very difficult.

**Insular Carcinoma versus Metastatic Neuroendocrine Carcinoma Grade III (Small Cell Carcinoma)**

Small cell carcinomas of the lung often metastasize to the thy-
roid (Fig. 10.18). Not infrequently, a rapidly growing thyroid
mass may be the only initial presenting sign of lung carcinoma.
Although the common denominator for both entities is the
small cell size, insular carcinoma cells lack the nuclear molding
and stretch artifacts, a hallmark of small cell carcinomas, but
extensive necrosis and frequent mitoses are common to both.
Also, small cell carcinoma cells usually have a pleomorphic nu-
clear pattern with round, oval, and oblong shapes, while insular
carcinoma cells are round. Insular carcinomas as well as small
cell carcinomas are TTF-1 and cytokeratin positive; however,
thyroglobulin is strongly expressed by insular carcinomas most
of the time, with rare exceptions.

**Insular Carcinoma versus Poorly Differentiated Metastatic Malignancy**

Poorly differentiated malignancy such as basaloid squamous
cell carcinoma may be extremely difficult to differentiate from
an insular carcinoma of the thyroid. Figure 10.19A, B represents
an example of such a case, whereby both the cytologic and the

### TABLE 10.1  Cytopathologic Features of Poorly Differentiated (Insular) Carcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellularity and presentation</td>
<td>Generally very cellular, malignant cells isolated, in loosely cohesive groups, or in syncytial tissue fragments; a dispersed pattern is frequent</td>
</tr>
<tr>
<td>Architecture</td>
<td>Syncytial tissue fragments of small malignant cells with follicular pattern, or forming insulae, nests, or trabeculae, intense crowding and overlapping of nuclei; peripheral palisading not present in the tissue fragments</td>
</tr>
<tr>
<td>Cells</td>
<td>Small, monomorphic</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Approximately 10 μm in diameter; round, deep-staining, granular chromatin with parachromatin clearing; single/multiple micronucleoli; no nuclear molding; mitoses ±; no stretch artifacts</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Scant, indiscernible; pale; vacuoles ±</td>
</tr>
<tr>
<td>Background</td>
<td>Clean to necrotic; features of preexisting follicular or papillary carcinoma ±</td>
</tr>
<tr>
<td>Immunocytochemical profile</td>
<td>Usually react positively with antibodies to thyroglobulin and TTF-1, occasionally negative; positive reactivity to cytokeratin; negative reactivity to calcitonin, neuroendocrine markers, leukocyte common antigen (LCA)</td>
</tr>
</tbody>
</table>

### TABLE 10.2  Differential Diagnosis of Insular Carcinoma

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary carcinoma with a small cell pattern</td>
</tr>
<tr>
<td>Other neuroendocrine tumors with small cells</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
</tr>
<tr>
<td>Metastatic small cell malignancy</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
</tr>
</tbody>
</table>

**Differential Diagnosis**

The differential diagnoses of insular carcinoma include neo-
plasms composed of small malignant cells such as: Medullary
thyroid carcinoma with a small cell pattern, other neuroen-
docrine tumors, namely, carcinoid tumors, or the recently
described noncalcitonin producing neuroendocrine carcinoma,
malignant non-Hodgkin lymphoma, metastatic malignancy
such as high-grade neuroendocrine carcinoma (small cell car-
cinoma), or poorly differentiated metastatic malignancy com-
posed of small cell pattern (Table 10.2). Immunostains are often
required to establish a correct diagnosis. The cytologic differen-
tiating features are listed in Table 10.3.

**Insular Carcinoma versus Medullary Thyroid Carcinoma**

The aspirate of a medullary carcinoma consisting of small,
uniform cells is very difficult to distinguish from insular
carcinoma of the thyroid without the help of immunostains
(Figs. 10.13 and 10.14). Insular carcinomas often show necrosis
and increased proliferative activity, a feature generally not ob-
served with medullary carcinomas. Calcitonin will be strongly
positive with medullary carcinoma cells. A rare primary neuro-
endocrine tumor referred to as calcitonin-free oat cell carcinoma

**Insular Carcinoma versus Medullary Thyroid Lymphoma**

A dispersed pattern of small malignant cells in an insular carci-
noma of the thyroid may be misinterpreted as malignant lym-
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an example of such a case, whereby both the cytologic and the
# Differential Diagnosis of Poorly Differentiated “Insular” Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Insular Carcinoma</th>
<th>Medullary Carcinoma Small Cell Type</th>
<th>Malignant Lymphoma</th>
<th>Metastatic Small Cell Carcinoma</th>
<th>Metastatic Basaloid Squamous Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Dispersed cell pattern or cells in syncytial tissue fragments forming nest, insulae, or trabeculae; microfollicular pattern ±; intense crowding and overlapping of nuclei</td>
<td>Neoplastic cells discrete, in loosely cohesive groups, infrequently in syncytial tissue fragments; pseudofollicular pattern ±</td>
<td>Cells mostly isolated with dispersed pattern; rare syncytial tissue fragment</td>
<td>Neoplastic cells isolated, in loosely cohesive groups and in syncytial tissue fragments without any architectural pattern</td>
<td>Neoplastic cells isolated, in loosely cohesive groups or in syncytial tissue fragments without any architectural pattern</td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Small in size, monomorphic, round, poorly defined cell borders; high N/C ratios</td>
<td>Small, monomorphic, poorly defined cell borders; high N/C ratios</td>
<td>Small, monomorphic, poorly defined cell borders; high N/C ratios</td>
<td>Small pleomorphic in size, poorly defined cell borders; high N/C ratios</td>
<td>Small, pleomorphic in size, poorly defined cell borders; high N/C ratios</td>
</tr>
<tr>
<td><strong>Nucleus</strong></td>
<td>Approximately 10 μm in diameter round; smooth nuclear membrane; finely granular chromatin with parachromatin clearing; micronucleoli +; no nuclear molding; no stretch artifacts; mitosis ±; intranuclear inclusions ±; nuclear groove ±; karyorrhexis not observed</td>
<td>Round; smooth nuclear membrane; coarsely granular chromatin; nuclei ±; nucleus often eccentric; no nuclear molding; no stretch artifacts; mitosis −; intranuclear inclusions ±; nuclear groove −; karyorrhexis −</td>
<td>Round; smooth to irregular nuclear membrane; finely granular chromatin with parachromatin clearing; micronucleoli +; no nuclear molding; mitosis +; stretch artifacts +; intranuclear inclusions −; nuclear groove −; karyorrhexis +</td>
<td>Round, oval, oblong to short spindle shape; smooth nuclear membrane; compact chromatin; nuclei ±; mitosis +; nuclear molding characteristics; stretch artifacts −; intranuclear inclusions −; nuclear grooves −</td>
<td>Rounds, oval to oblong; smooth nuclear membrane; chromatin coarsely granular and deep staining; nuclei ±; no nuclear molding; mitosis −; stretch artifacts −; intranuclear inclusions −; nuclear grooves −</td>
</tr>
<tr>
<td><strong>Cytoplasm</strong></td>
<td>Scant, insignificant; may contain small vacuoles</td>
<td>Scant, insignificant; rudimentary cytoplasmic tailing</td>
<td>Scant, indiscernible</td>
<td>Scant, indiscernible</td>
<td>Scant; indiscernible</td>
</tr>
<tr>
<td><strong>Colloid</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Amyloid</strong></td>
<td>Absent</td>
<td>±</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td>Clean or necrosis</td>
<td>Clean</td>
<td>Clean or necrotic debris</td>
<td>Necrosis</td>
<td>Necrosis ±</td>
</tr>
<tr>
<td><strong>Immunoprofile</strong></td>
<td>Thyroglobulin +</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>TTF-1 +</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Calcitonin −</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine markers −</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>LCA −</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
FIGURE 10.13. FNA of a medullary thyroid carcinoma depicting syncytial tissue fragments composed of monomorphic small cells with hyperchromatic nuclei. In the absence of a typical pleomorphic cell pattern of a medullary carcinoma, a diagnosis of insular carcinoma must be considered. A positive calcitonin stain will establish the diagnosis.

FIGURE 10.14. A. A medium-power view of an aspirate of a medullary thyroid carcinoma showing small monomorphic malignant cells appearing discohesive and in syncytial tissue fragments resembling insulae. B. Higher magnification. The malignant cells are small with insignificant cytoplasm, high N/C ratios. Note pseudofollicular pattern (arrows). Such a pattern with small cells may be mistaken for an insular carcinoma. C. Histologic section of the medullary carcinoma showing nests of small, round-to-cuboidal cells. The tumor cells strongly reacted to calcitonin.
FIGURE 10.15.  A. FNA of a thyroid mass. The aspirate is markedly cellular, consisting of several syncytial tissue fragments as well as loosely cohesive cells (low power). B. Higher magnification showing the syncytial tissue fragment of the malignant cells without any architectural pattern. The malignant cells have scant, undifferentiated cytoplasm. Their nuclei are slightly larger than the usual insular carcinoma cells and bear a strong resemblance to neuroendocrine carcinoma cells. C. The cell block of the aspirate showing several tissue fragments forming insulae. There is marked necrosis in the background (medium power). D. Higher magnification demonstrating an insular pattern. The tumor cells did not express thyroglobulin, TTF-1, calcitonin, or any neuroendocrine markers. Only cytokeratin was positive. The neoplasm strongly resembles a small cell neoplasm, but the exact morphologic type remains undetermined. This may represent an endocrine carcinoma (clinically serum calcitonin levels were not elevated).

FIGURE 10.16.  FNA of a primary malignant lymphoma of the thyroid. The monomorphic cell population of poorly differentiated lymphoid cells closely resembles cells of insular carcinoma. The malignant lymphoma cells will react positively with leukocyte common antigen (LCA).

FIGURE 10.17.  FNA of a primary malignant lymphoma of the thyroid showing a syncytial tissue fragment bearing morphologic resemblance to insular carcinoma.
a high nuclear/cytoplasmic ratio, syncytial tissue fragments with and without a follicular pattern, granular chromatin with micronucleoli. Accurate cytologic diagnosis is difficult and usually made on histologic examination.

SUMMARY

Insular carcinomas constitute a subset of poorly differentiated thyroid carcinomas, with aggressive behavior, and present a characteristic histocytopathologic pattern. Criteria helpful in correct identification include small monomorphic cells with a high nuclear/cytoplasmic ratio, syncytial tissue fragments with and without a follicular pattern, granular chromatin with micronucleoli. Accurate cytologic diagnosis is difficult and usually made on histologic examination.

REPORTING THE CYTOLOGIC FINDINGS

Author Recommendation:
Malignant: Consistent with poorly differentiated thyroid carcinoma.
BSRTC:
Malignant: Consistent with poorly differentiated thyroid carcinoma.

histologic presentation appeared to closely resemble that of an insular carcinoma. The diagnosis of insular carcinoma was not supported by the negative reactivity to follicular cell markers such as thyroglobulin or TTF-1. An extensive workup confirmed a basaloid squamous cell carcinoma arising in the esophagus that had invaded the thyroid and presented itself as a thyroid mass.

FIGURE 10.18. A, FNA of a metastatic small cell carcinoma of the lung, which presented as a thyroid mass. The malignant cells exhibit a typical cytologic pattern of small cell carcinoma. Note round, oval, oblong nuclei with molding. The cytoplasm is insignificant. Also note stretch artifacts and karyorrhexis. B, The cell block of the aspirate confirming small cell carcinoma.

FIGURE 10.19. A, FNA of a metastatic basaloid squamous cell carcinoma of the esophagus that presented as a rapidly growing thyroid mass. The aspirate is cellular, showing syncytial tissue fragments of small uniform malignant cells with scant cytoplasm and high N/C ratios. Note necrosis in the background. The pattern is highly suggestive of an insular carcinoma. B. The cell block of the aspirate showed malignant cells presenting an insular pattern and considerable necrosis. Note the peripheral palisading (arrows) of nuclei, which is not a feature of insular carcinoma. The differential diagnoses included insular carcinoma, medullary carcinoma, and a metastatic small cell carcinoma. The tumor cells expressed only cytokeratin. Further investigations revealed an infiltrating basaloid squamous carcinoma of the esophagus that infiltrated the thyroid, presenting as a goiter. (Courtesy of Mithra Baliga, MD, University of Mississippi, Jackson, MS.)
REFERENCES


SUGGESTED READINGS