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Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation

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There are many controversies involving the diagnostic criteria and treatment of well-differentiated thyroid carcinoma. Vascular invasion has been identified as an important and independent prognosticator in many cancers. The majority of pathologists recognize the importance of vascular invasion as a diagnostic marker of malignancy in follicular lesions of thyroid; however, several reports have suggested that angioinvasion is not a predictor of bad prognosis in thyroid carcinomas. We suggest that the criteria for diagnosing angioinvasion in thyroid carcinomas as well as in other endocrine tumors are inconsistent and the controversy may be attributed to application of inappropriate criteria. We carried out a study of a potential cause of artefactual vascular invasion in a series of autopsy thyroids and established the morphology of mimics of angioinvasion. We then reviewed retrospectively the clinicopathological features of a series of 4000 thyroid carcinomas of follicular epithelial derivation to identify the features and significance of the most rigid criteria of vascular invasion: tumor cells invading through a vessel wall and thrombus adherent to intravascular tumor. These features were identified in 118 (3%) lesions. Follow-up information was available for 98 patients. Of these, 35% developed distant metastases. When using the rigid criteria, ~1/3 of angioinvasive well-differentiated thyroid carcinomas and 1/2 of angioinvasive poorly differentiated thyroid carcinomas developed distant metastases at a mean 5.3 years of follow-up. Our results indicate that the application of rigid criteria for vascular invasion provide a clinically relevant prediction of distant metastasis in patients with thyroid carcinomas, especially in well-differentiated thyroid carcinomas.
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The diagnosis of well-differentiated thyroid carcinoma is based on the presence of diagnostic nuclear features of papillary thyroid carcinoma or capsular and/or vascular invasion by a follicular epithelial neoplasm.[1–4] There are many controversies involving the diagnostic criteria, treatment and follow-up assessment of well-differentiated thyroid carcinoma that usually has an indolent biological course.[5–8] Current risk stratification schemes used in the management of patients with well-differentiated thyroid carcinoma do not adequately incorporate the prognostic implications of detailed pathological features such as vascular invasion, mitoses, tumor cell necrosis, extra-thyroidal extension, histological subtypes and the molecular biological profile of the primary tumor.[7,9] Among the histopathological parameters, vascular invasion has been reported as an important and independent prognosticator in many other head and neck cancers. Although the majority of pathologists recognize the importance of vascular invasion in the diagnosis of malignancy in thyroid follicular lesions, several reports have suggested that angioinvasion is not a predictor of bad prognosis in thyroid carcinomas.[10–13] This may be because the criteria for diagnosing angioinvasion in thyroid carcinomas as well as in other endocrine tumors are poorly defined.

To address this problem, we examined the clinicopathological features of a large series of thyroid carcinomas derived from follicular epithelium to

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determine the criteria for vascular invasion that have clinical significance.

Materials and methods

A series of 4000 thyroid carcinomas derived from follicular epithelium were obtained from the files of University Health Network between September 2001 and August 2009. This series included 3841 (96%) papillary thyroid carcinomas, 17 (0.4%) follicular thyroid carcinomas, 84 (2.1%) poorly differentiated thyroid carcinomas and 58 papillary thyroid carcinomas with focal dedifferentiation where <10% of the lesion was poorly differentiated (1.5%). An additional eight anaplastic thyroid carcinomas identified were excluded from the study. Patient age, gender and pathologic features including tumor size, histological tumor type and variant were reviewed. The clinical charts of these patients were reviewed to determine the presence of distant metastasis during follow-up.

The cases were reviewed for features that are considered criteria of angioinvasion, including the following:

- Tumor cells in vascular spaces.
- Tumor cells underlying endothelium of vascular channels.
- Tumor cells invading through a vessel wall and endothelium.
- Thrombus adherent to intravascular tumor.

Examples of the first two features were identified in a large number of cases. The presence of tumor cells in vascular spaces was associated with features that suggested manipulation of the gland.

To determine whether this was possibly attributed to artifact, a series of thyroid nodules identified at autopsy was manipulated by exerting pressure on the lesion and subsequently submitting the capsule of the lesion to serial sectioning and microscopic examination.

The immunohistochemical markers anti-CD31 and D2-40 were used for distinguishing vascular invasion from lymphatic invasion or pseudoinvasion when required.

Results

Artefactual Displacement of Tumor Cells

The study of thyroid nodules manipulated at autopsy included five examples of benign lesions, all follicular nodular disease or follicular adenoma including one Graves' disease and Hashimoto thyroiditis. The features of these disorders were all characterized by macrofollicular architecture, bland cytology and minimal to no stromal fibrosis. Despite the benign features, displacement of tumor cells was identified following manipulation. Large vessels in or immediately beyond the capsule of the manipulated lesion contained tumor cells within the lumen, usually in small groups (Figures 1a and b). In some cases, tumor cells were seen bulging into the vascular space under intact endothelium (Figure 1c). There was no evidence of tumor invading through the endothelium associated with these foci. Most importantly, there was no evidence of fibrin thrombus, even with large fragments of intraluminal tumor (Figure 1d).

Features of Angioinvasion in Thyroid Carcinomas

In a large number of cases, there were conspicuous areas where a tumor mass was identified bulging into the vascular lumen, lined by intact endothelial cell layer (Figures 2a and b). Also frequently identified were tumor cell clusters covered by endothelium, even floating loosely within a vascular channel (Figure 2c). The latter can easily be explained as the point of branching of a vessel. Artefactual tumor cell implants (Figure 2c) and florid reactive endothelial cell proliferation (Figure 2d) were often identified at the site of previous needle biopsy. There was no correlation between the presence of these features and the subsequent development of metastatic disease, and these were therefore not interpreted as evidence of angioinvasion.

In contrast, the most rigid criteria: (i) tumor cells invading through a vessel wall and endothelium and (ii) thrombus adherent to intravascular tumor (Figure 3) were found in 118 of 4000 (3%) thyroid carcinomas derived from follicular epithelium (Table 1). These tumors from 118 patients (37 males, 81 females, ages 22–84, mean 52.39 years) and ranged from 0.8 cm to 11.5 cm (mean 5.08 cm). They included 83 well-differentiated thyroid carcinomas (70%), 22 poorly differentiated thyroid carcinomas (19%) and 13 well-differentiated thyroid carcinomas with focal dedifferentiation (11%; Table 2). The extent of angioinvasion was not more than two foci and in most of the cases, only a single focus was observed.

Significance of Angioinvasion in Thyroid Carcinomas

Follow-up information was available for 98 of the 118 cases; no information was available for 5 follicular variant papillary thyroid carcinomas, 5 oncocytic follicular variant papillary thyroid carcinomas, 3 classical variant papillary thyroid carcinomas and 7 poorly differentiated thyroid carcinomas. The follow-up time ranged from 18 months to 10 years (mean 5.3 years).

Among the 98 patients, distant metastases were documented in 34 patients (35%). The most common metastatic sites were lung (32 patients), bone (12 patients), brain (2 patients) and liver (2 patients). Distant metastasis originated from 20 angioinvasive well-differentiated thyroid

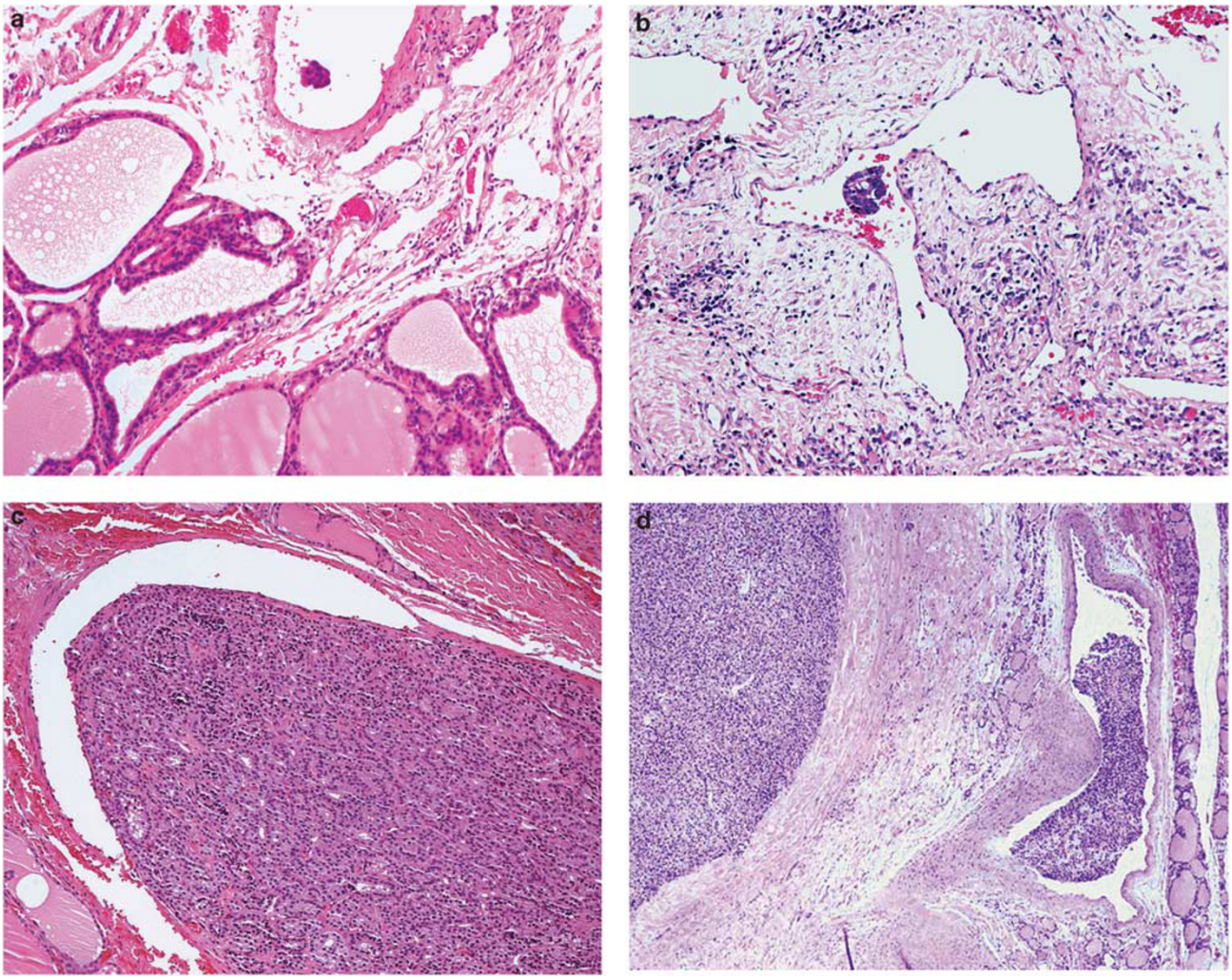

Figure 1 Thyroid gland manipulated at autopsy by mechanical compression showing pseudoangioinvasion: Graves' disease and Hashimoto thyroiditis with artefactual displacement of thyroid follicular epithelial cells within the vascular lumen, respectively (**a**, **b**); follicular adenoma bulging under the intact endothelium (**c**); artefactual displacement of the follicular epithelial cells from a follicular adenoma (**d**).

carcinomas (59%), 7 angioinvasive poorly differentiated thyroid carcinomas (21%) and 7 angioinvasive well-differentiated thyroid carcinomas with focal dedifferentiation (21%). Thus, 29% of angioinvasive well-differentiated thyroid carcinoma, 54% of well-differentiated thyroid carcinomas with focal dedifferentiation and 47 % of poorly differentiated thyroid carcinomas developed distant metastases (Table 3). In the angioinvasive well-differentiated thyroid carcinoma group, 52% of angioinvasive follicular variant papillary thyroid carcinomas, 26% of angioinvasive classical papillary thyroid carcinomas and 14% of angioinvasive tall cell papillary thyroid carcinomas developed distant metastases (Table 3). When all tumors with any degree of dedifferentiation were grouped, 50% (14/28) of angioinvasive thyroid carcinomas with any poorly differentiated carcinoma component developed distant metastases.

Discussion

As Graham's first description,[14] microscopic vascular invasion has been a source of controversy in surgical pathology of the thyroid. It was initially a critical element in the diagnosis of follicular thyroid carcinoma. The last few decades have seen a decrease in the incidence of follicular thyroid carcinoma. In areas of endemic goitre, this may be a consequence of dietary iodine supplementation, but in many parts of the world, the significant change in incidence of follicular thyroid carcinoma can be attributed to increasing recognition of the diagnostic cytological features of follicular variant papillary carcinoma.[1]

Several reports have suggested that angioinvasion is not predictive of bad prognosis in thyroid carcinomas.[10–13] However, the criteria applied in these reports may be inappropriate. In fact, the

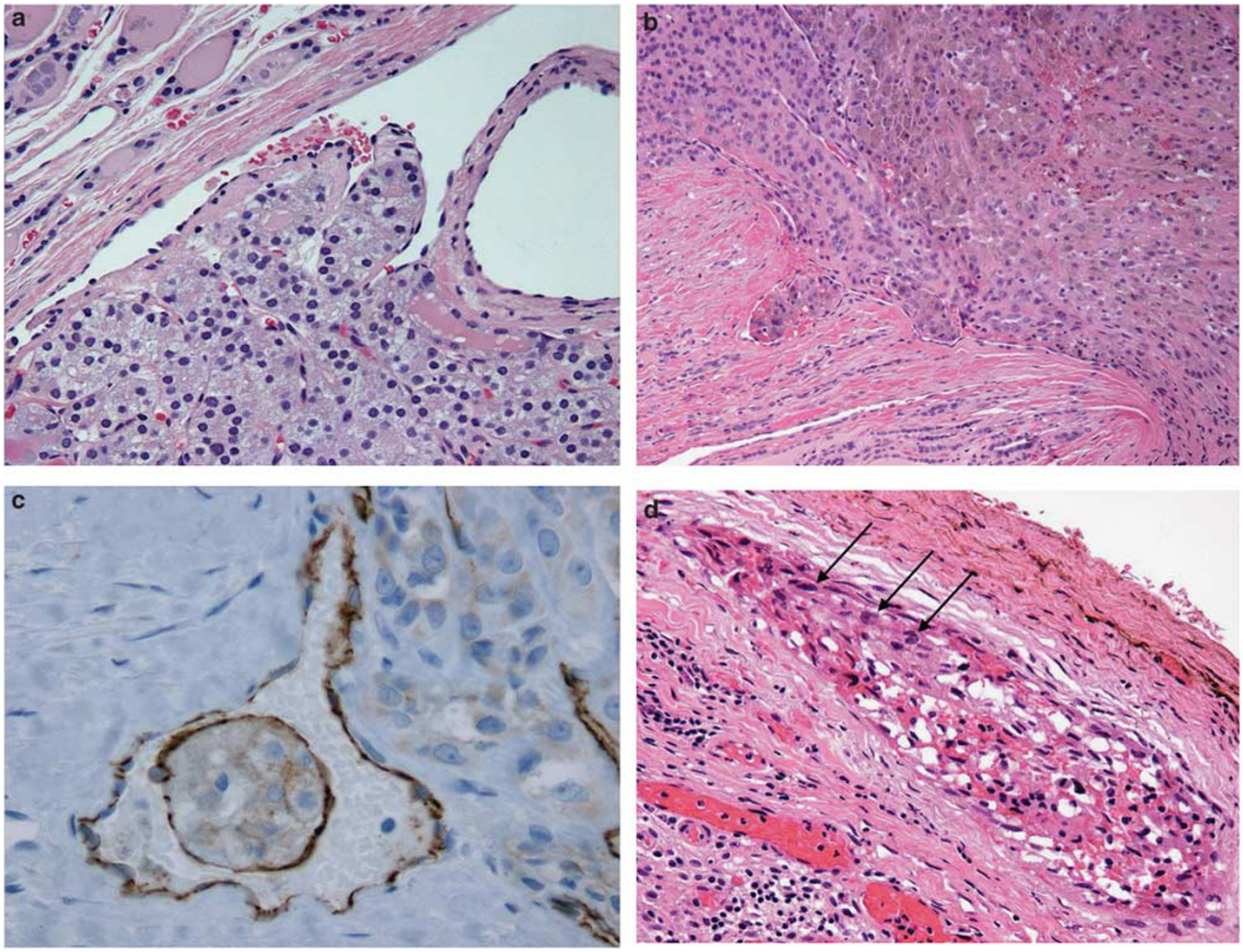

Figure 2 Pseudoangioinvasion characterized by a bulging tumor mass lined with an intact endothelial cell layer (**a**); artefactual displacement of tumor cells clusters after FNA (**b**); tumor cells covered by intact endothelium, anti-CD34 (**c**); and florid reactive endothelial cell proliferation (**d**, arrows).

definition of angioinvasion in endocrine tumors is a common diagnostic problem, as evidenced by the fact that well-differentiated pancreatic endocrine tumors with angioinvasion in the absence of gross local invasion and/or distant metastasis were regarded as 'well-differentiated endocrine tumor with uncertain behavior' in the WHO 2004 classification.[2]

The term 'lymphovascular invasion' is listed in the synoptic pathology checklist for thyroid carcinomas that has been approved by the College of American Pathologists. On the basis of our data, we recommend separation of lymphatic from vascular invasion. Differentiated thyroid carcinomas, most often papillary thyroid carcinomas, are associated with frequent lymph node metastasis and generally have an indolent behavior. Lymphatic vessel invasion is thought to correlate with lymph node metastasis, whereas blood vessel invasion may be associated with hematogenous dissemination that predicts poor outcome in thyroid cancer. Therefore, unlike other cancers, it is biologically important to separate lymphatic invasion from angioinvasion in this disease. The differences in pathologist interpretation of criteria for angioinvasion[1–4,15,16] are not surprising, given the fact there are many controversies in the surgical pathology of thyroid gland.

Classical criteria for diagnosing angioinvasion include (i) tumor bulging under intact endothelium, (ii) intravascular tumor nests covered with endothelium, (iii) tumor casts or emboli in the blood vessel lumen, (iv) tumor cells invading through a blood vessel wall and (v) thrombus adherent to intravascular tumor.[1–4,15,16] To understand these criteria, one must understand the biology of vascular dissemination of tumor cells.[17] This is a multistep process initiated by migration of tumor cells from the primary site, followed by destruction of the vascular basement membrane including the endothelial cell layer.[17] Tumor cells that invade blood vessels enter into vascular channels and tend to aggregate in clumps within the circulation,[17] initiating the

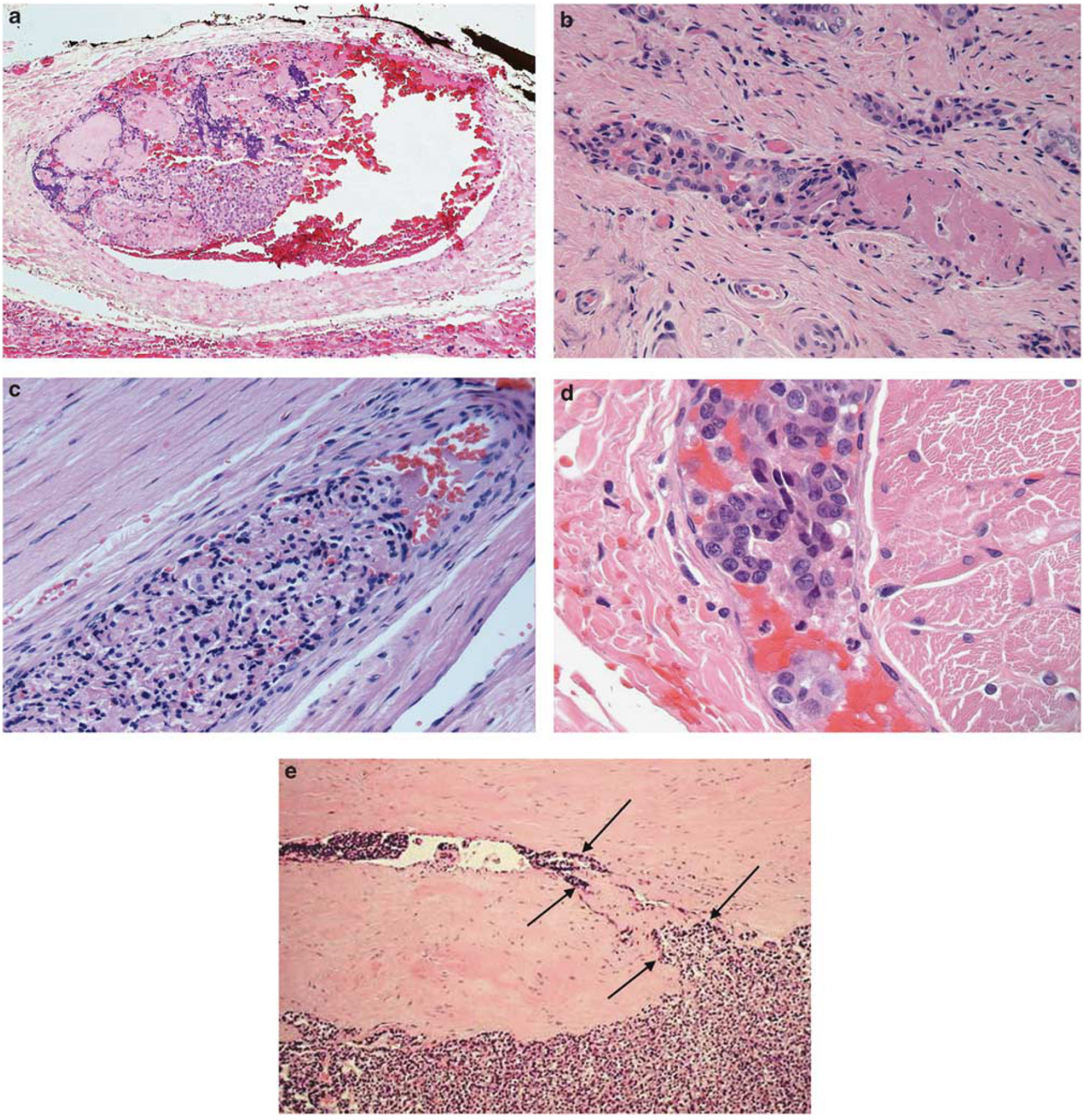

Figure 3 Clinically significant or 'true' angioinvasion is characterized by tumor cells invading through a vessel wall (arrows) and thrombus adherent to intravascular tumor (**a–e**).

formation of platelet–tumor aggregates. It is also important to note that tumor cells simultaneously activate coagulation factors that result in the formation of tumor cell emboli.[17] In fact, all steps are essential for stabilizing tumor cells within the circulation in order to enhance tumor cell survival and implantability.[17]

Both experimental data and clinical investigations have revealed that platelets and thrombin promote hematogenous metastasis.[17–25] Cancer cells produce tissue factors and procoagulant factors that activate the extrinsic coagulation pathway.[21,22] Surface adhesion molecules and β3 integrins in particular have a major role in mediating these specific interactions.[24] However, activation of factor X results when tumor cells react with factor VII and this process results in the production of thrombin–tumor cell complexes.[21,22] The presence of thrombus is essential for stabilization of intravascular tumor cells and implantability.[17] Moreover, it has been demonstrated that

Table 1 Classification of 118 angioinvasive thyroid carcinomas

Histopathology	n/N *(%)* *118/4000 (3%)*[a]
Well-differentiated thyroid carcinoma	83/3858 (2.2)
Papillary thyroid carcinoma	81/3841 (2)
Follicular thyroid carcinoma	2/17 (12)
Papillary thyroid carcinoma with focal dedifferentiation	13/58 (22)
Poorly differentiated thyroid carcinoma	22/84 (26)

[a]Total rate of angioinvasive thyroid carcinomas in this series.
n: total number of angioinvasive carcinoma for each tumor type.
N: total number of cases for each tumor type.

Table 2 Histopathological distribution of 83 angioinvasive well-differentiated thyroid carcinomas

Histopathology	n *(%)*
Papillary thyroid carcinoma	81 (98)
Classical variant	26 (31)
Follicular variant	20 (24)
Oncocytic follicular variant	14 (17)
Clear cell follicular variant	1 (1)
Mixed classical and follicular variant	3 (4)
Tall cell variant	7 (8)
Solid variant	5 (6)
Warthin-like variant	2 (2)
Cribriform and morular variant	2 (2)
Diffuse sclerosing variant	1 (1)
Follicular thyroid carcinoma	2 (2)

Table 3 Distant metastases in 98 angioinvasive thyroid carcinomas with follow-up data

Total distant metastases	n/N *(%)* *34/98 (35%)*[a]
Well-differentiated thyroid carcinoma	20/70 (29)
Follicular variant papillary thyroid carcinoma	13/25 (52)
Classical variant papillary thyroid carcinoma	6/23 (26)
Tall cell variant papillary thyroid carcinoma	1/7 (14)
Well-differentiated thyroid carcinoma with focal dedifferentiation	7/13 (54)
Poorly differentiated thyroid carcinoma	7/15 (47)

[a]The overall rate of distant metastases in angioinvasive thyroid carcinoma that had available follow-up information.
n: the number of angioinvasive thyroid carcinomas that developed distant metastases; the total number of patients with documented distant metastases is 34.
N: the number of angioinvasive thyroid carcinomas that had available follow-up information; the total number for this category is 98.

administration of anti-coagulant therapy, such as low molecular weight heparins, delays tumor progression and has a significant anti-metastatic role.[18,20,23,25]

It is therefore important to identify fibrin–tumor cell thrombus in areas of vascular invasion. Fibrin cannot be reliably identified by ultrastructural studies and fibrin thrombus may not be obvious on conventional H&E stained slides; however, immunolocalization of fibrin and/or fibrinogen can be helpful.[19]

The thyroid gland is supplied by a very rich endocrine vascular network.[26,27] There is no or little fibrous stroma between follicular epithelial cells and blood vessels.[27,28] Moreover, the endothelium of endocrine glands is very thin and fenestrated. This accounts for the artefactual mimic of angioinvasion that we could reproduce by manipulation of benign lesions and is not unlike the iatrogenic lesions described in gynecological pathology as a result of mechanical manipulation at the time of surgery.[29] Histological vascular pseudoinvasion can result from stromal retraction, peliosis, previous biopsy or aggressive surgery, sectioning and handling of the specimen. Only the presence of thrombus adherent to intravascular tumor can distinguish true angioinvasion from pseudoinvasion.

As a consequence of the thin fenestrated endocrine endothelium, bulging of follicles within nodules is seen even in benign follicular nodular disease, but does not constitute a criterion for vascular invasion.[1–4] For this reason, angioinvasion is assessed within the capsule or beyond the capsule of the lesion; but not within tumor nodules.[1–4] In our experience, bulging of tumor islands under endothelium even in the capsule does not qualify as clinically significant angioinvasion if the endothelium is intact (Figures 1c and 2a).[1]

Aida *et al*[15] demonstrated two types of veins in the capsule of follicular lesions: horizontal type veins, which extend along the capsule showing a poststenotic dilatation, and vertical type veins that flow directly outside the capsule showing a mild dilatation. They were able to demonstrate that vascular invasion is observed along the horizontal type veins at the poststenotic focus in follicular thyroid carcinomas. Moreover, by carrying out a 3-D analysis of vascular invasion in follicular thyroid carcinoma, they showed that intravascular tumor nests covered by intact endothelium and as well as tumor that extends as a subendothelial layer are not true vascular invasion (Figures 2a–c). This report is consistent with the current understanding of tumor biology.[17] In contrast, endothelialisation of tumor cells is important when tumor cells reach their sites of distant metastasis in order to finalize extravasation and invasion of the subendothelial matrix.

Another artifact is florid intravascular endothelial hyperplasia, which can be seen in the capsular vessels following biopsy. This change is characterized by a proliferation of plump spindle-shaped endothelial cells and pericytes intermingled with red blood cells and thrombus (Figure 2d).[3,4]

Several studies highlight that the determination of the number of foci of vascular invasion is of clinical

significance in patients with follicular tumors and the presence of four or more foci of vascular invasion (extensive vascular invasion) is regarded to have a significant recurrence rate.[6,30] However, in our series all patients with angioinvasive differentiated thyroid carcinomas that developed distant metastases revealed predominantly a single focus of angioinvasion and there were no more than two foci of vascular invasion. Thus, the use of appropriate criteria seems to be more critical than the number of involved vessels, as patients with a single focus of true angioinvasion developed metastatic lesions in our series.

Vascular invasion is reported in 2 to 47% of papillary thyroid carcinomas.[10–13,31–33] Nishida *et al*[33] reported vascular invasion in 46.9% of papillary thyroid carcinomas and distant metastases in only 8% of angioinvasive papillary thyroid carcinomas, suggesting that the criteria applied were not specific enough to identify high risk patients. Our review identified rigid criteria of vascular invasion in only 3% of thyroid carcinomas. The rate of distant metastasis from thyroid carcinoma in Ontario is $<1\%$ (data provided by Cancer Care Ontario), therefore, the expected number of patients with distant metastases in our series is <40 patients. Interestingly, we were able to demonstrate that with these rigid criteria, 34 cases developed distant metastasis at a mean 5.3 years of follow-up, making this a highly predictive feature.

We documented distant metastasis in 35% of angioinvasive thyroid carcinomas. When excluding poorly differentiated thyroid carcinoma and papillary thyroid carcinomas with evidence of dedifferentiation, we found angioinvasion in only 2.2% of cases. Of note, 29% of angioinvasive well-differentiated thyroid carcinomas, 54% of well-differentiated thyroid carcinomas with focal dedifferentiation and 47% of poorly differentiated thyroid carcinomas developed distant metastases. Interestingly, 52% of angioinvasive follicular variant papillary thyroid carcinomas developed distant metastases in our series. On the other hand, regardless the extent of dedifferentiation, 50% of angioinvasive thyroid carcinomas with a poorly differentiated carcinoma component developed distant metastases. As the development of metastatic disease can be as late as 10 years and our mean follow-up is less than this period of time, the development of additional distant metastases can be predicted over the coming years and thus will have impact on the percentage of metastatic disease in our angioinvasive thyroid carcinoma series.

In conclusion, our results indicate that the application of rigid criteria to identify vascular invasion predicts distant metastasis in patients with thyroid carcinomas, especially in well-differentiated thyroid carcinomas. When using these rigid criteria, $\sim 1/3$ of angioinvasive well-differentiated thyroid carcinomas and 1/2 of angioinvasive poorly differentiated thyroid carcinomas developed distant metastases in a mean of 5.3 years of follow-up. Those rigid criteria include identification of tumor cells invading through a vessel wall and identifying thrombus adherent to intravascular tumor. Other features, such as tumor cells within vascular lumena unassociated with thrombus, and tumor cells underlying intact endothelium, represent pseudoinvasion and are not valuable in predicting metastatic spread. This issue is of clinical significance, as angioinvasion should be considered a feature that dictates more aggressive postoperative treatment and surveillance.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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