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Case study

Follicular thyroid carcinoma with an unusual glomeruloid pattern of growth ☆

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Summary We describe an uncommon thyroid tumor in a 56-year-old woman. The widely infiltrating, angioinvasive neoplasm, 5 cm in diameter, exhibited a peculiar architectural growth pattern characterized by follicles with round to oval epithelial tufts growing within, often supported by a fibrovascular core mimicking the renal glomerulus. Colloid-empty follicles, tubular or elongated, were lined by pseudostratified tall, columnar cells with clear cytoplasm. Nuclei were round to oval, with evenly distributed, slightly coarse chromatin. Tumor cells were positive for thyroid transcription factor-1, thyroperoxidase, thyroglobulin, cytokeratin 18, Hector Battifora mesothelial cell, and vimentin. Scattered cells positive for S100, Wilms tumor 1 (WT1), and cytokeratins AE1/AE3 were found, with no reaction detected for cytokeratins 34βE12, 5/6, 7, 19, or 20. There were *PAX8-PPARγ* rearrangement and *N-RAS* mutation. No mutations were found for *APC* or *BRAF* genes, nor were *RET/PTC* rearrangements detected. Because of the distinctive histologic features, we propose naming this tumor *follicular thyroid carcinoma with an unusual glomeruloid pattern of growth*.

1. Introduction

In the most recent *World Health Organization Classification of Tumors of Endocrine Organs*, published in 2004 [1], follicular cell–derived carcinomas are broadly classified into well-differentiated (papillary and follicular carcinomas), poorly differentiated, and undifferentiated carcinoma on the basis of histologic and clinical parameters. This classification in several tumor types is strongly supported by advances in

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molecular studies showing the involvement of distinct genes in these tumor categories, with little overlap.

The term glomeruloid refers to an architectural pattern of growth that mimics the renal glomerulus; this term also includes some patterns that could be described as tufted and knotted growth and a more complex intraglandular pseudocribriform pattern with prominent microvessels [2]. We present the first report of a peculiar follicular cell–derived carcinoma with a hitherto undescribed glomeruloid pattern of growth and striking negativity for a broad range of cytokeratins (CKs). Histologically, this neoplasm may be misdiagnosed as the cribriform-morular variant of papillary thyroid carcinoma (PTC), columnar cell carcinoma, poorly differentiated carcinoma (PDC) of the thyroid, and even as a metastasis in the thyroid of a peculiar neoplasm (eg, Wilms tumor). We think that this tumor is a rare variant of follicular carcinoma, which we propose terming the *glomeruloid variant*. However, more reported cases are necessary to confirm this tumor histotype as a morphological entity.

2. Case report

A 56-year-old woman presented with a right thyroid nodule of unknown duration. There was no history of previous radiation to the head and neck region, familial adenomatous polyposis (FAP), or other endocrine disorders. Right lobectomy (plus isthmectomy) was performed; grossly, the specimen showed a solid, partially encapsulated nodule measuring 40 × 50 mm with some invasive nodules in the adjacent thyroid measuring less than 5 mm. The surgical specimen was fixed in neutral, phosphate-buffered, 10% formalin, and paraffin-embedded sections were stained with hematoxylin and eosin. Immunohistochemical studies were performed on 4-μm-thick paraffin sections using a peroxidase-conjugated labeled-dextran polymer (Dako EnVision Peroxidase/DAB; Dako, Glostrup, Denmark) to avoid misinterpreting endogenous biotin or biotin-like activity in cell cytoplasms or nuclei as positive staining. Antibodies, dilutions, suppliers, pretreatment, and immunostaining results are listed in Table 1.

For molecular genetic analysis, genomic DNA was extracted from the paraffin-embedded tumor tissue using QIAamp DNA Mini Kit (QIAGEN, The Netherlands) following the manufacturer's instructions. We screened for mutations in exons 11 and 15 of the *BRAF* gene (NM_004333). Exon 11 was amplified by polymerase chain reaction (PCR) using the forward primer 5′-GCATAAGGTAATGTACTTAGGGTGAA-3′ and the reverse primer 5′-AACAGTGAATATTTCCTTTGATGAT-3′, whereas for exon 15, the following primers were used: forward, 5′-TCATAATGCTTGCTCTGATAGG-3′; reverse, 5′-GGCCAAAAATTTAATCAGTGGA-3′. Primers were previously designed with the Primer3 Input program (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi). PCR conditions were as follows: denaturation step at 94°C for 3 minutes followed by 35 cycles at 94°C for 30 seconds, 30 seconds of annealing at 60°C for exon 15 and at 55°C for exon 11, and 72°C for 45 seconds, and a final extension at 72°C for 7 minutes. PCR products were bidirectionally sequenced in capillary electrophoresis (ABI3730, Applied Biosystems, Forest City, CA) using the aforementioned primers. *N-RAS* exon 2 primers and PCR conditions were as previously published [3]. Seven sets of primers, as previously reported [4], were used to amplify, by PCR analysis, the regions of the *APC* gene where germ line mutations in FAP with associated thyroid carcinomas have been described.

RET/PTC rearrangement detection was investigated with fluorescence in situ hybridization (FISH) using the procedure of Marques et al [5] on isolated nuclei. DNA probe generation from 3 yeast artificial chromosome clones (313F4, 214H10, 344H4) covering the *RET* locus and probe hybridization were performed as detailed in an earlier report [6] and kindly provided by Professor Horst Zitzelsberger. Detection of digoxigenin-labeled YAC probe (344H4) was carried out using an antidigoxigenin fluorescein antibody (Roche Diagnostics GMbH, Manheim, Germany) and the biotinylated labeled YAC probe (214H10, 313F4) with CY_3-avidin (Jackson Immunoresearch Lab, West Grove, PA, USA). Fluorescence hybridization signals were then analyzed and recorded with a Cytovison System (Applied Imaging, New Castle, UK). At least 200 cell nuclei were scored for the presence of a split FISH signal (rearranged) in addition to an overlapping signal (normal). Only cells with either 2 overlapping signals or 1 split and 1 overlapping signal were counted to ensure that only complete cell nuclei had been scored.

Detection of *PAX8-PPAR*γ rearrangement was investigated with FISH using the procedure of Marques et al [5] on isolated nuclei. BAC probes for PPARγ (RPCI1130 G23, BAC PAC Resources) and PAX8 (RPCI 1165 I12, BAC PAC Resources) were used. Detection of digoxigenin-labeled PPARγ probe was carried out using an antidigoxigenin fluorescein antibody (Roche Diagnostics GMbH) and the biotinylated labeled PAX8 probe with CY_3-avidin (Jackson Immunoresearch Lab). Fluorescence hybridization signals were then analyzed and recorded with a Cytovison System. For each case, 200 intact nonoverlapping nuclei were counted. Nuclei in which the 2 probes were fused or touching were scored as positive for fusion gene.

Epidermal growth factor receptor (*EGFR*) was also investigated with FISH using a standard procedure with fluorescent-labeled dual-colored probes (LSI EGFR/CEP7 Vysis, Downers Grove, IL, USA) according to the manufacturer's protocol. A SpectrumRed-labeled EGFR-specific probe hybridizes to the EGFR locus on chromosome 7 at 7p12, and a SpectrumGreen-labeled centromeric probe binds to the centromere of chromosome 7 as a control to normalize copy numbers. At least 30 tumor cells selected from 4 different areas were analyzed. Amplification is determined as a ratio of *EGFR* to centromere of chromosome 7 signal of 2 or more per cell.

Table 1 Antibodies, dilutions, suppliers, and results of immunohistochemical staining

Antigen	Antibody clone and source	Dilution	Pretreatment	Results
TTF-1	8G7G3/1, Dako, Glostrup, Denmark	1:20	Water bath, 20 min	+n
Thyroglobulin	DAK-Tg6, Dako	1:2000	None	+c *
Thyroperoxidase	MoAb47, Dako	1:50	Microwave, 20 min	+c *
Calcitonin	Polyclonal/BioGenex, San Ramon, CA, USA	1:5000	None	–
Chromogranin A	DAK-A3, Dako	1:200	Microwave, 20 min	–
Synaptophysin	SY38/BioGenex	1:1000	Microwave, 20 min	–
CKs 1, 2, 10, 11, 14, 15, 16, and 19	AE1/AE3, Dako	1:20	Microwave, 20 min	+c *
CKs 1, 5, 10, and 14	34βE12, Dako	1:50	Microwave, 20 min	–
CKs 5 and 6	D5/16 B4, Dako	1:100	Microwave, 20 min	–
CK 7	OV-TL 12/30, Dako	1:50	Microwave, 20 min	–
CK 18	DC 10, Dako	1:50	Microwave, 20 min	+c
CK 19	RCK108, Dako	1:100	Microwave, 20 min	–
CK 20	K_s20.8, Dako	1:20	Microwave, 20 min	–
EMA	E29, Dako	1:50	Microwave, 20 min	–
Hector Battifora mesothelial cell	HBME-1, Dako	1:200	Water bath, 20 min	+m
Vimentin	V9, BioGenex	1:10 000	Microwave, 20 min	+c
S100 protein	Polyclonal, Dako	1:5000	Microwave, 20 min	+c, n *
Desmin	D33, Dako	1:10	Microwave, 20 min	–
α-Estrogen receptor	6F11, Novocastra	1:5	Water bath, 20 min	–
β-Estrogen receptor	Polyclonal, Santa Cruz, CA, USA	1:50	Water bath, 20 min	+n
Progesterone receptor	PgR 636, Dako	1:50	Water bath, 20 min	–
Androgen receptor	AR441, Dako	1:100	Water bath, 20 min	+n
WT1	6F-H2, Dako	1:10	Water bath, 20 min	+c *
E-Cadherin	36, Transduction Lab, KY, USA	1:2000	Microwave, 20 min	+m *
β-Catenin	β-Catenin-1, Dako	1:300	Microwave, 20 min	+m
Bcl-2 oncoprotein	124, Dako	1:5	Water bath, 20 min	+c
Galectin-3	9C4, Novocastra, Newcastle upon Tyne, UK	1:200	None	–
Carcinoembryonic antigen	Polyclonal, Dako	1:2000	None	–
HER2 protein (c-erbB-2)	Herceptest, Dako	Prediluted	Water bath, 20 min	–
EGFR	EGFR pharmDx, Dako	Prediluted	Protease	+m
c-kit (CD117)	c-kit pharmDx, Dako	Prediluted	Microwave, 20 min	–
CD10	C5C6, Novocastra	1:10	Microwave, 20 min	–
CD31	JC70A, Dako	1:10	Microwave, 20 min	–
Cyclin D1	SP4, Master Diagnostica, Granada, Spain	Prediluted	Microwave, 20 min	–
P63 protein	4A4, Dako	1:10	Water bath, 20 min	–
p53 protein	DO-7, Novocastra	1:20	Microwave, 20 min	–
P27	1B4, Novocastra	1:20	Water bath, 20 min	–
Ki-67	MIB-1, Dako	1:200	Water bath, 20 min	5%

Abbreviations: m, membranous; c, cytoplasmic; n, nuclear staining pattern.
* Weak and/or focal staining.

After histologic diagnosis, total resection of the left thyroid lobe was performed, and an ablative dose of $^{[131]}$I was given. The patient was well 12 months after the diagnosis, without evidence of FAP on endoscopic evaluation.

3. Results

Histologic examination revealed a partially encapsulated tumor, with neoplastic nodules penetrating through the capsule infiltrating the adjacent thyroid tissue (Fig. 1A). There were also unequivocal signs of vascular invasion (Fig. 1B). The neoplasia showed a peculiar architectural growth pattern characterized by follicles with round to oval epithelial tufts growing within the follicles, at times supported by a fibrovascular core mimicking the renal glomerulus (Figs. 1 and 2). Follicles were empty of colloid, tubular or elongated in shape, and lined by pseudostratified tall columnar cells, with clear cytoplasm showing supranuclear and subnuclear vacuoles (Fig. 2). Nuclei were round to oval with evenly distributed, slightly coarse chromatin and absent or inconspicuous nucleoli.

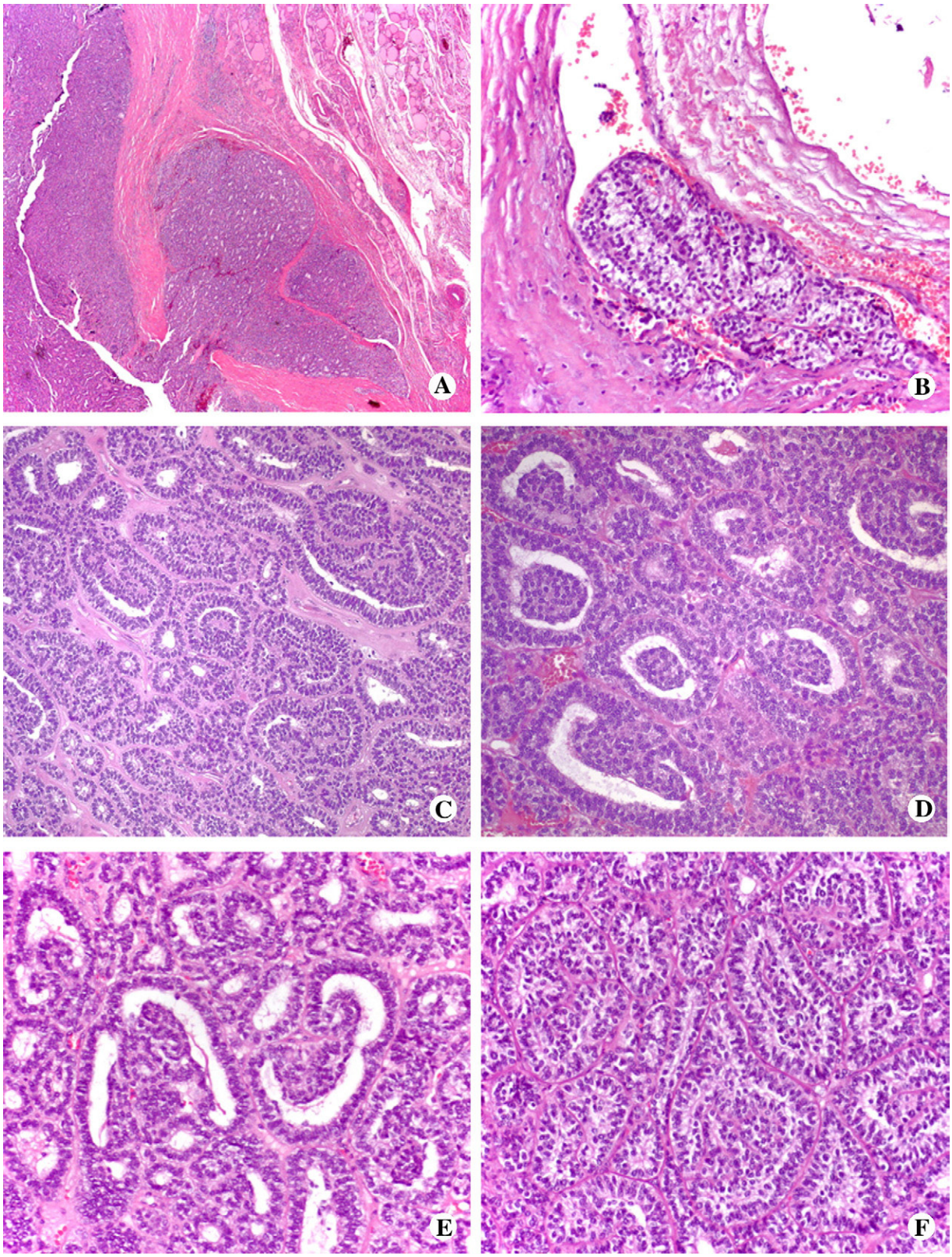

Fig. 1 Glomeruloid variant of follicular carcinoma. A peculiar growth pattern with glomeruloid features (C-F), complete penetration of the capsule (A), and vascular invasion (B) was found. (Magnification: (A) ×40; (B) ×200; (C) ×100; (D–F) ×200.)

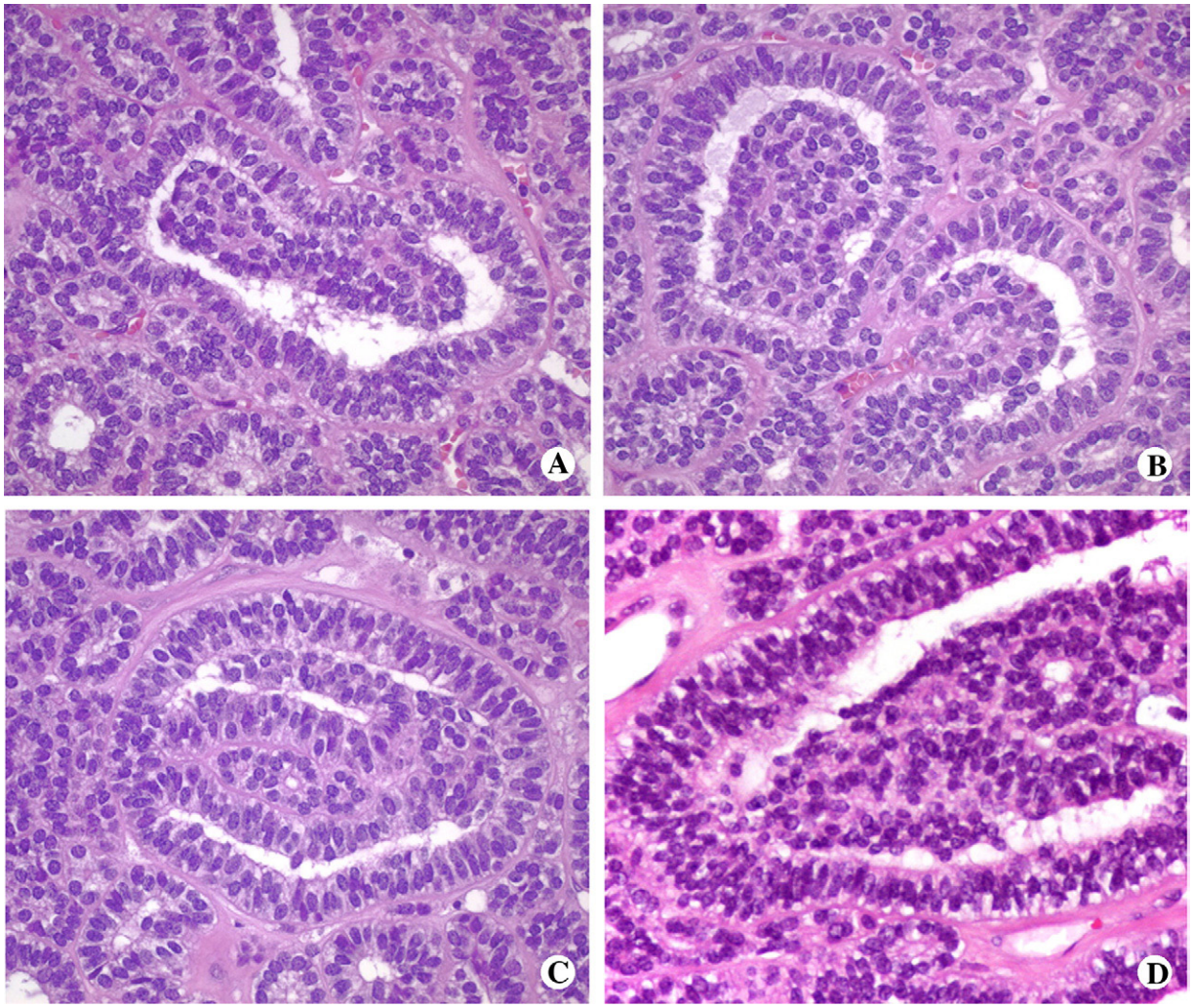

Fig. 2 Glomeruloid variant of follicular carcinoma. The glomeruloid structures have a layer of "visceral" epithelium covering the epithelial tuft (A-D). A prominent vascular core is also seen in panel (B). (Magnification ×400.)

Discrete overlapping was detected, but no other nuclear features typical of PTC were present. Throughout the nodule, there was minimal atypia and less than 2 mitotic figures per 10 high-power field. Irregular calcifications and focal hyalinization without necrosis were found in some areas of the tumor. The thyroid parenchyma outside the tumor was histologically normal with a focus of florid intravascular endothelial proliferation adjacent to the tumoral capsule.

The results of the immunohistochemical study are summarized in Table 1. The tumor cells showed reactivity for thyroid transcription factor-1 (TTF-1), thyroglobulin, tyroperoxidase (TPO), CK 18, Hector Battifora mesothelial cell (HBME-1), vimentin, β-estrogen receptor, androgen receptor, bcl-2, EGFR, and β-catenin (Fig. 3). The reaction for thyroglobulin was weak, patchy, and mainly along the luminal border of the cytoplasm (Fig. 3C). Faint, patchy E-cadherin expression and very faint, focal immunoreactivity for TPO and AE1/AE3 were found; a few, different, scattered cells positive for S100 and WT1 were also detected (Fig. 3D). No immunoreaction was noted for calcitonin, chromogranin, synaptophysin, and CKs 34βE12, 5/6, 7, 19, 20 (Fig. 3A); nor was there any positivity for epithelial membrane antigen (EMA), desmin, α-estrogen receptor, progesterone receptor, galectin-3, carcinoembryonic antigen, HER2 protein, c-kit (CD117), CD10, cyclin D1, p63, p53, or p27. A vascular core was highlighted by CD31 stain in some glomeruloid structures. The proliferative index in the neoplasia, evaluated by MIB-1, was 5%.

In the mutational study of the *APC* gene, we were unable to amplify exon 3 and codon 848 (exon 15); no mutations were detected in the other analyzed regions of the *APC* gene. No *RET/PTC* rearrangements, *BRAF* gene mutations, or *EGFR* gene amplification were detected. A mutation in exon 2 of *N-RAS* was found. The mutation in codon 61 consisted of a CAA > CGA change that leads to a substitution of glutamine by an arginine (p.Q61R).

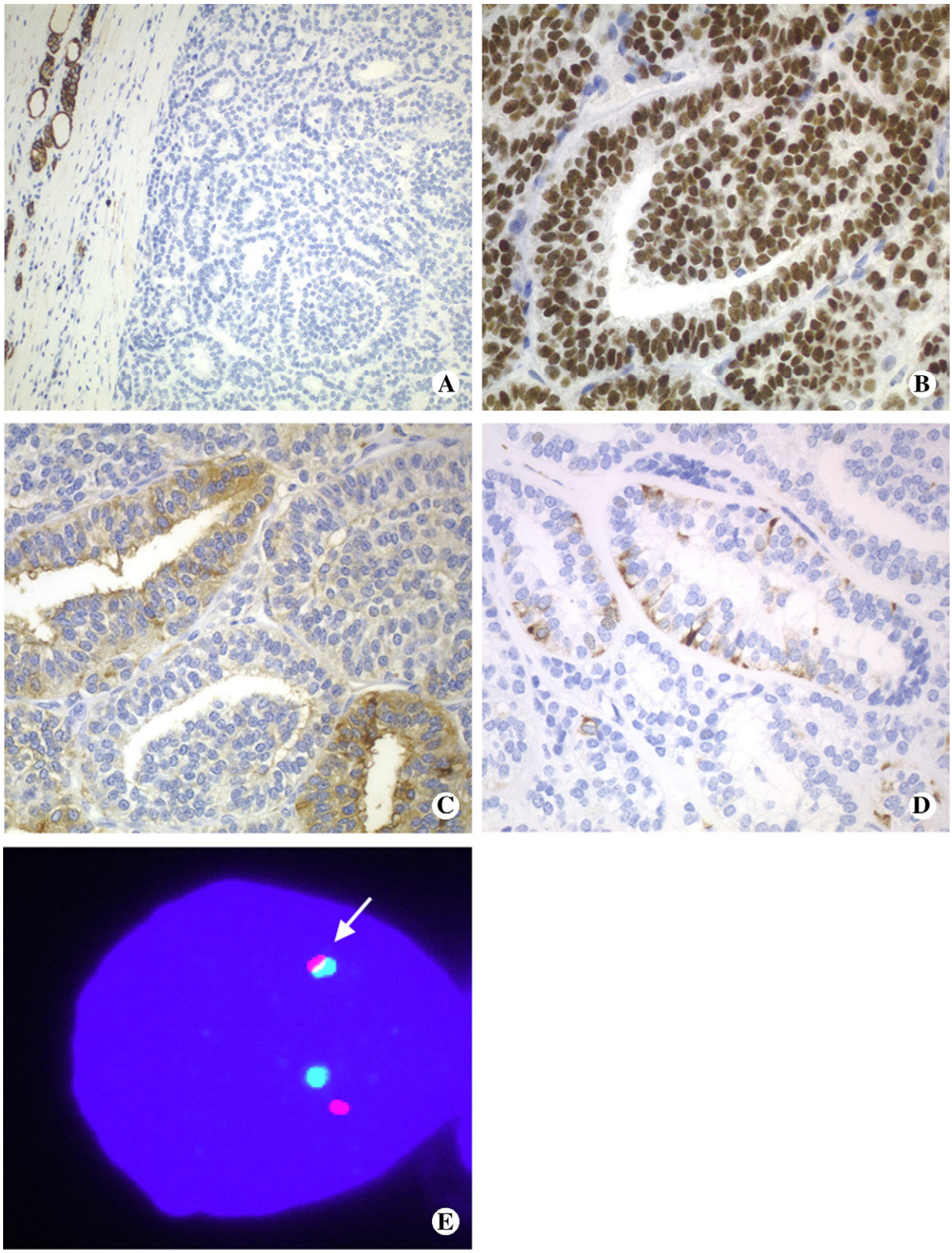

Fig. 3 Glomeruloid variant of follicular carcinoma. Tumor cells are negative for CK 7 (A), but immunoreactivity for TTF-1 (B), thyroglobulin (C), and WT1 protein (D) was detected. Representative result obtained in the FISH analysis for PPARγ and PAX8 is seen in panel (E). Green dots are the BAC probes for PPARγ, red dots are BAC probes for PAX8; the nuclei is stained with DAPI. Nuclei in which the 2 probes were fused or touching were scored as positive for fusion gene (arrow). (Magnification: (A) ×100; (B–D) ×400; (E) ×1000.)

PAX8-PPARγ rearrangement was observed in 20% of the 200 nuclei analyzed (Fig. 3E).

4. Discussion

Here, we describe an unusual, widely infiltrating, angioinvasive thyroid carcinoma of follicular cells with a glomeruloid pattern of growth and negativity for a broad range of CKs, which we propose naming glomeruloid variant. Because of its peculiar features, this tumor can be misdiagnosed as the cribriform-morular variant of PTC, columnar cell carcinoma, PDC of the thyroid, or a metastatic carcinoma.

The cribriform-morular variant of PTC [4] is the term coined for the sporadic type of PTC, which is morphologically indistinguishable from most of the thyroid carcinomas that arise in the setting of FAP. This PTC variant is histologically characterized by a mixture of cribriform, follicular, papillary, trabecular, solid, and spindle cell patterns of growth, with morular foci showing peculiar nuclear clearing (biotin rich nuclei); at the molecular level, there are somatic *RET/PTC* rearrangements as well as alterations in the Wnt signaling pathway [4,7]. In the present tumor, clinical data of FAP, morular structures with characteristic positivity for CD10, alterations in the *APC* gene and/or aberrant nuclear location of *β*-catenin were not found [4,7,8]. Columnar cell carcinoma of the thyroid also shows significant morphologic overlap with our case (pseudostratified columnar cells, some of which may contain supranuclear and subnuclear cytoplasmic vacuoles reminiscent of those of early secretory endometrium, solid areas, and elongated and empty follicles resembling tubular glands), but this case differs specifically in the lack of papillae, the presence of glomeruloid structures, and the immunoprofile of CKs [1]. PDC has a solid/trabecular/insular pattern of growth and lacks the conventional features of PTC, partially mimicking the present case; however, at variance with PDC [9], our case displays a low mitotic index and no necrosis (nor has a glomeruloid appearance been described in any PDC). A metastatic origin for the present tumor can be easily excluded based on the immunohistochemical findings, that is, the positivity for TTF-1, thyroglobulin, and TPO [1].

Glomeruloid structures consisting of anastomosing proliferations of capillary blood vessels resembling the glomerular rete arteriosus are characteristic of high-grade astrocytic tumors [10], and glomerulus-like epithelial aggregates have also been described in rare cases of prostatic adenocarcinoma [11]. Prostatic adenocarcinoma with glomeruloid features is usually seen in high-grade adenocarcinoma [11], but a similar pattern has been recognized in ductal carcinoma in situ of the human female breast [12]. More recently, a diffuse biphasic pleural-based malignant tumor with immature blastematous elements, glomeruloid epithelial structures, and focal WT1 expression has been published [13]. To the best of our knowledge, the present case represents the first thyroid tumor with glomeruloid features. Strong nuclear immunohistochemical expression for WT1 is seen in the blastemal cells of the nephrogenic zone of the fetal kidney as well as in differentiating glomeruli [14]. Within the adult kidney, WT1 expression is limited to the parietal and visceral glomerular epithelium, whereas the presence of WT1 positivity in a renal tumor supports the diagnosis of nephroblastoma or desmoplastic small round cell tumor [14]. Nephroblastoma (Wilms tumor), a malignant embryonal neoplasm of the kidney, shows various histologic components with diverse cells that may express variable degrees of differentiation that represent various stages in normal or abnormal nephrogenesis [14]. The discovery of the *WT1* as the causative gene in an autosomal-recessive condition identified it as a tumor suppressor gene; however, this view is not in keeping with the frequent finding of wild-type, full-length WT1 in human leukemia, breast cancer, prostate cancer, and several other cancers including most Wilms tumors [15]. In fact, the study of both the *WT1* mRNA expression levels and the intensity of staining of WT1 protein in normal thyroid tissue and thyroid tumors indicates an important role of the wild-type *WT1* gene in the tumorigenesis of primary thyroid cancer [16]. In the present case, both "glomeruloid" structures and "embryonal" tubular follicles suggest a "blastomatoid tumor" that could share pathogenetic alterations with nephroblastoma, but the expression of WT1 was only cytoplasmic and very limited.

In addition to the glomeruloid pattern, the limited positivity for CKs is also an intriguing finding of the present tumor. EMA, clone AE1/AE3, and CKs 7, 8, 19, and 20 are all negative in the renal glomerulus, suggesting that our case replicates the antigenic composition of the glomerulus, but the positivity for CK 18 in our case does not support this assumption [14]. Well-differentiated and poorly differentiated follicular cell–derived carcinomas are positive for low-molecular-weight CKs [1]. About 80% of the cases of undifferentiated (anaplastic) carcinomas are also positive for the AE1/AE3 CK antibody "cocktail." In some follicular carcinomas, as in rare follicular adenomas, there is focal immunoreactivity for CK 19 in contrast to the widespread immunostaining observed in PTC. A lower expression of keratins and thyroglobulin, with E-cadherin down-regulation and strong expression of vimentin, was reported in a (well-differentiated) spindle cell variant of PTC and interpreted as mesenchymal-like metaplasia [17]. In the present case, the histologic features exclude undifferentiated carcinoma and the negativity for a broad range of CKs and EMA seems to reflect more a lack of epithelial differentiation than dedifferentiation.

Trying to situate the glomeruloid variant within the frame of the World Health Organization classification of thyroid tumors [1], we know that the most distinctive molecular features of follicular carcinoma are the high prevalence of *RAS* mutations and *PAX8-PPARγ* rearrangement [18]. At variance with follicular carcinoma, the PTC shows a series of functionally similar and mutually exclusive alterations such

as *BRAF* mutation, *RET/PTC* and *TRK* rearrangements, or *RAS* mutation. Other alterations playing a role in PTC pathogenesis are c-met overexpression and down-regulation of E-cadherin expression [18]. The absence of nodal metastasis despite the local and vascular invasiveness of the tumor, the peculiar CK pattern and the detection of *PAX8-PPARγ* rearrangement, and *N-RAS* mutation, combined with the absence of *BRAF* mutation and *RET/PTC* rearrangement, support the glomeruloid variant being a subtype of follicular carcinoma rather than of papillary carcinoma. Negativity for p53 fits with a well-differentiated thyroid neoplasm and the increased expression of EGFR, with reduced $p27^{KIP1}$ expression, may be correlated with tumor progression [1,18], thus fitting with the prominent invasive features of the present case.

In summary, this study draws attention to a rare type of unusual thyroid tumor that could possibly run the risk of being misdiagnosed but which seems to be a variant of follicular carcinoma. Because of its distinctive histologic and immunohistochemical features, we propose naming this tumor histotype the *glomeruloid variant of follicular carcinoma*. However, more reported cases are necessary before consider this neoplasm as a special category.

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