Original Article

Paucicellular Variant of Anaplastic Thyroid Carcinoma

A Mimic of Riedel's Thyroiditis

SUK-KING WAN, FRCPA, JOHN K.C. CHAN, MRCPATH, AND SIU-KIN TANG, MB, CHB

Anaplastic thyroid carcinomas usually pose no problems in histologic diagnosis because of the obvious invasive growth, high cellularity, and frank anaplasia. Two cases of a variant of anaplastic thyroid carcinoma with peculiar gross and histologic features closely mimicking those of Riedel's thyroiditis are described in this report. The clinical features were no different from those of the usual anaplastic thyroid carcinomas: occurrence in elderly subjects, presentation with rapidly enlarging neck mass associated with compression symptoms, and rapidly fatal outcome. The tumors were infiltrative, hard, fibrotic masses that partly or completely replaced one lobe of the thyroid, and extended to perithyroid tissues. Histologically, they were predominated by acellular fibrous or infarcted tissue with central dystrophic calcification, as well as hypocellular foci comprising mildly atypical spindle cells intermingled with collagen and small lymphocytes. Both cases showed permeation and plugging of the arteries by tumor. Lymph node metastasis was documented in one case. The spindle cells were positive for epithelial membrane antigen in both cases, and cytokeratin in one. The qualifying term "paucicellular variant" accurately describes this uncommon morphologic variant of anaplastic thyroid carcinoma. It is important to recognize this variant so as not to mistaken it for Riedel's thyroiditis, which is a reactive condition with a very favorable prognosis. The distinguishing features are as follows: presence of infarction, atypical cells in at least some areas, atypical spindle cells obliterating large blood vessels, and immunoreactivity for epithelial markers. (Key words: Thyroid neoplasm; Anaplastic thyroid carcinoma; Riedel's thyroiditis) Am J Clin Pathol 1996;105:388–393.

Anaplastic thyroid carcinoma comprises 5% to 10% of all thyroid cancers, typically occurs in elderly subjects, and is associated with a highly aggressive clinical course.[1–8] Histologically, it is characterized by polygonal cells, giant cells, and spindle cells that are present in variable proportions.[1,5–8] In most cases, the histologic diagnosis of these highly cellular, pleomorphic, and mitotically active tumors is easy. We report two cases with unusual histologic features and very low cellularity, closely mimicking Riedel's thyroiditis, and propose designating this the "paucicellular" variant. This term is adopted from the legend for an illustration of anaplastic thyroid carcinoma that appears in LiVolsi's book, *Surgical Pathology of The Thyroid*.[6]

CASE REPORTS

Case 1

A 54-year-old Chinese woman presented with a hard neck mass for 6 months associated with left vocal cord paralysis. Total thyroidectomy was performed because of a clinical diagnosis of thyroid carcinoma. The histologic diagnosis made at that time was Riedel's thyroiditis. The patient died 1 year after surgery, and no autopsy was performed.

Case 2

A 85-year-old Chinese woman presented with a neck mass for 2 months, associated with dysphagia and hoarseness of voice. A thyroid nodule and a hard cervical lymph node were found. Fine-needle aspiration was performed twice on both lesions, and yielded mainly fibrous tissue and some bland-looking spindle cells, with no definitive diagnosis being made. At surgery, the thyroid was found to be fixed to the trachea and esophagus. A 1 cm piece of tissue taken for intraoperative frozen section was reported to be a fibrous lesion, possibly Riedel's thyroiditis; however, anaplastic carcinoma could not be ruled out. A thyroid lobe containing the lesion and a cervical lymph node were then received for histologic analysis, and a final diagnosis of anaplastic carcinoma was made. The patient received one course of post-operative radiotherapy. She was well at the last follow-up 10 months after the operation. The patient then defaulted follow-up, and died 25 months after diagnosis, but no autopsy was performed.

MATERIALS AND METHODS

The two cases were identified in the histopathology files of Queen Elizabeth Hospital, Hong Kong, through the years 1976 to 1994. The specimens had been fixed in buffered formalin and processed in the usual way for paraffin embedding. Four μm thick sections were cut and stained with hematoxylin and eosin. Selected sections

From the Department of Pathology, Queen Elizabeth Hospital, Kowloon, Hong Kong.

Manuscript received August 24, 1995; revision accepted October 11, 1995.

Address reprint requests to Dr. Suk-King Wan: Department of Pathology, Queen Elizabeth Hospital, Wylie Road, Kowloon, Hong Kong.

were stained with elastic van Gieson. Immunohistochemical studies were performed using the avidin-biotin-peroxidase complex technique. The antibodies used included those against cytokeratin (MNF116, Dakopatts), monoclonal carcinoembryonic antigen (A5B7, Dakopatts, Glostrup, Denmark), epithelial membrane antigen (E29, Dakopatts), thyroglobulin (antiserum, Dakopatts), calcitonin (antiserum, Dakopatts), muscle-specific actin (HHF35, Enzo Biochem, New York, NY) and desmin (D33, Dakopatts). Appropriate positive and negative controls were included.

PATHOLOGIC FINDINGS

Gross Findings

Both cases were similar. A 4.5 cm grayish-white firm mass with irregular borders was present in one lobe. The central portion was stony-hard and yellow due to hyalinization and calcification. The lymph node in case 2 was similarly made up of hard white tissue. The remaining thyroid gland was unremarkable for case 1, but little normal thyroid tissue was seen in the specimen from case 2.

Histologic Findings

The most striking impression on histologic examination was an infiltrative lesion with large areas of fibrosis and foci of calcification (Fig. 1). Although there were areas of genuine sclerosis, many of the "sclerotic" areas in fact represented infarcted tissue, as evidenced by total lack of stainable cells and the ghost shadow outlines of blood vessels (Fig. 1B and 2). Interspersed throughout was a hypocellular spindle cell proliferation that showed an interlacing fascicular or storiform pattern (Fig. 3). The spindle cells had relatively bland nuclei and indistinct nucleoli, and mitotic figures were rare. They were intermixed with abundant collagen fibers and some small lymphocytes (Fig. 4). At the periphery, there were areas with slightly higher cellularity, mild to moderate nuclear pleomorphism and increased mitotic activity (Fig. 5). The interface with the surrounding tissue was sharp or infiltrative (Fig. 6), with entrapment of thyroid follicles. The thyroid follicular epithelium did not exhibit oncocytic changes (Fig. 4). In both cases, there was unequivocal tumor plugging and obliteration of the arteries, a phenomenon that was easier to appreciate in an elastic stain (Fig. 7). The residual thyroid tissue appeared unremarkable. A differentiated thyroid carcinoma component could not be identified despite extensive histologic sampling.

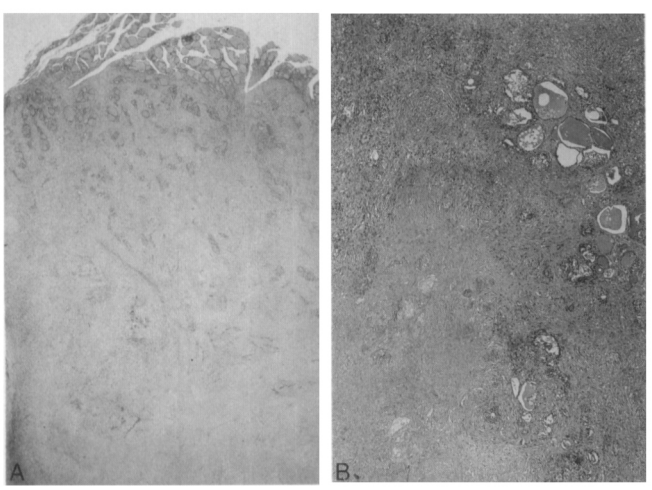

FIG. 1. Low magnification appearance of tumor. A, The tumor is infiltrative and remarkably hypocellular (case 2). B, The tumor infiltrates between the thyroid follicles, and exhibits acellular zones (left lower field) due to infarction (case 1).

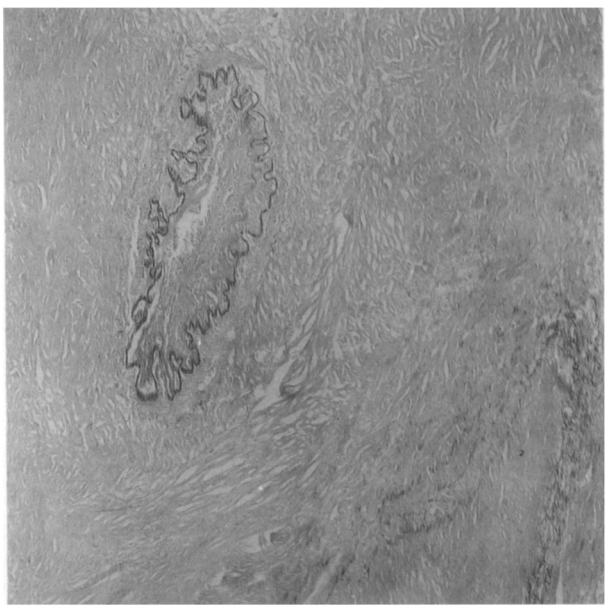

FIG. 2. The acellular areas originate from an infarction process, as evidenced by the presence of ghost shadows of blood vessels (case 2).

The lymph node of case 2 was almost completely replaced by hyalinized and infarcted tissue, with a narrow rim of viable tumor at the periphery (Fig. 8).

Immunohistochemical Findings

In case 1, the tumor cells were negative for all markers tested except for EMA and muscle-specific actin. For case 2, there was staining for cytokeratin, EMA, and actin, but not the other markers (Fig. 7C).

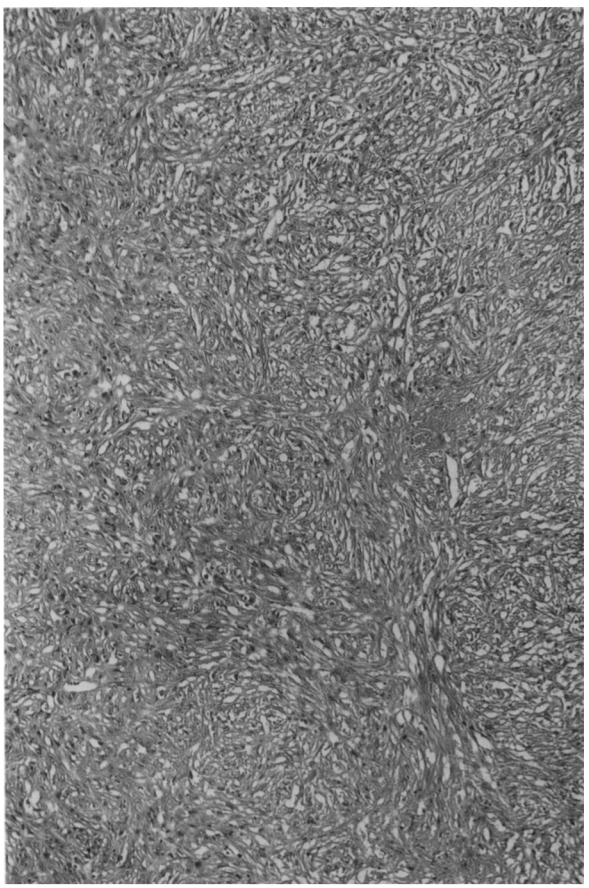

FIG. 3. In the low cellularity areas, the spindly cells and collagen interact to produce a storiform pattern (case 1).

DISCUSSION

Riedel's thyroiditis is a very rare, chronic inflammatory fibrosclerotic lesion with a favorable prognosis.[6,9,10] This condition was first recognized in 1883 by Berhard Riedel, who later published three such cases.[9,10] Since then, approximately 200 cases have been reported in the English literature. Although it has been suggested that Riedel's thyroiditis may represent a late form of Hashimoto's thyroiditis or De Quervain's disease,[11,12] this entity now is widely considered to be a distinct entity and to show a strong association with scleroinflammatory processes of other sites, such as the mediastinum,[14] retroperitoneum,[15-20] bile ducts,[20,21] and orbit.[22-26] Because of the rarity of Riedel's thyroiditis, few pathologists have sufficient personal experience with this entity. As indicated by Schwaegerle and colleagues, the incidence of Riedel's thyroiditis appears to have dramatically decreased in recent decades,[27] suggesting that this disease has become less prevalent or that there was an over-diagnosis in the past. It is likely that some reported cases of Riedel's thyroiditis might have represented fibrosing variant of Hashimoto's thyroiditis or anaplastic thyroid carcinoma.

In contrast to Riedel's thyroiditis, anaplastic carcinoma is less uncommon and constitutes 5% to 10% of all thyroid carcinomas. Because it is one of the most aggressive malignant tumors, a correct diagnosis and distinction from Riedel's thyroiditis is of great importance. Clinically, anaplastic thyroid carcinoma and Riedel's thyroiditis do share many similarities, rendering accurate preoperative distinction very difficult: both show strong female predominance, broad age range (although the mean age of anaplastic thyroid carcinoma is in mid 60s and that of Riedel's thyroiditis is late 40s), and presentation as rapid onset of a hard thyroid mass associated with compression symptoms and fixation to adjacent structures.[1-8] In the great majority of cases, a histologic diagnosis can be readily made because of obvious atypia in the tumor cells. The paucicellular variant, as described in this study, is liable to be mistaken for Riedel's thyroiditis on histologic assessment. The first case in this report

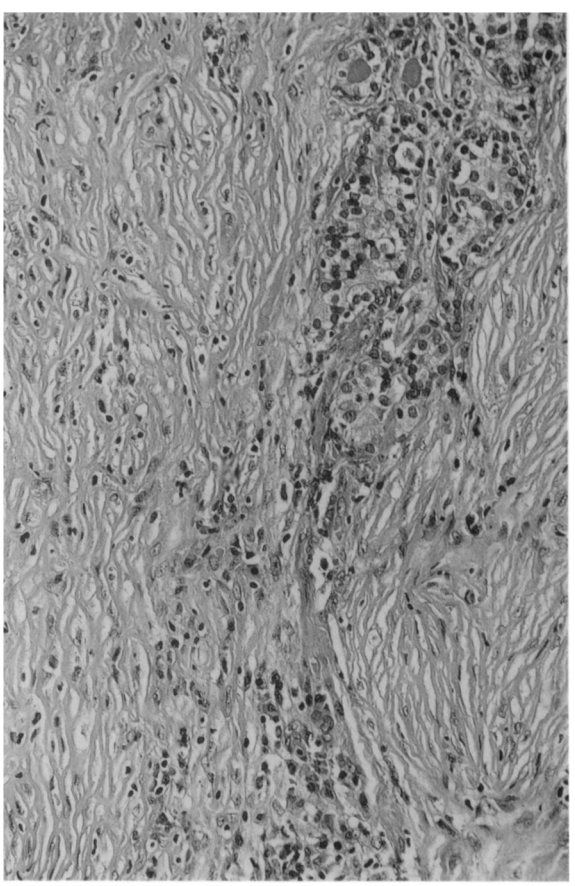

FIG. 4. The marked sclerosis, hypocellularity and lymphoplasmacytic infiltrate result in an appearance highly suggestive of Riedel's thyroiditis or sclerosing Hashimoto's thyroiditis. However, oncocytic changes typical of the latter are not seen (case 2).

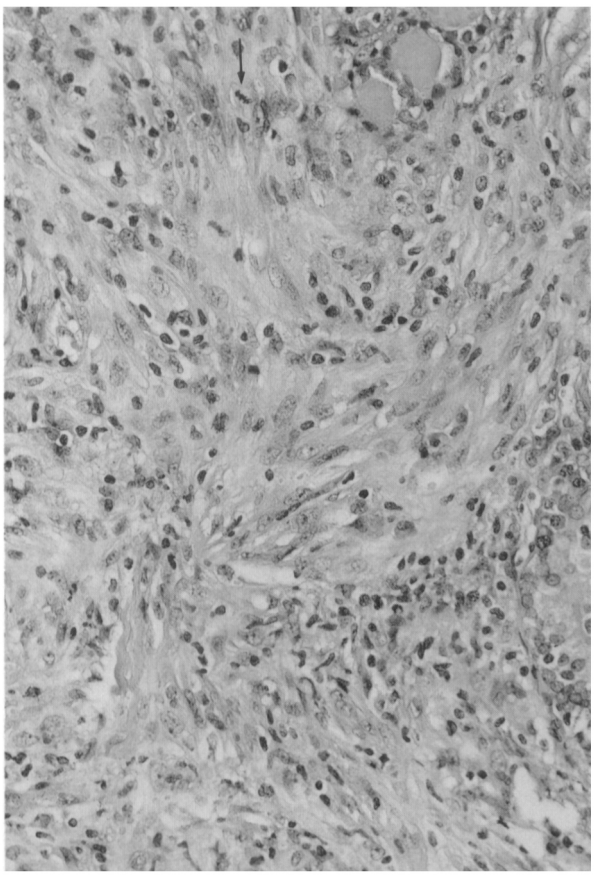

FIG. 5. Slightly more cellular areas characterized by spindly cells which resemble myofibroblasts. Nuclear atypia is subtle. Occasional mitotic figures (arrow) are seen. Note the sprinkling of lymphocytes, heightening the mimicry of an inflammatory process (case 2).

was originally misdiagnosed as Riedel's thyroiditis. It was recovered from the only example of "Riedel's thyroiditis" in our files. In the second case, the possibility of Riedel's thyroiditis was seriously considered during diagnostic evaluation. The diagnoses made on this case by a panel of pathologists in a slide exchange club were as follows: Riedel's thyroiditis (5 responses); benign mesenchymal proliferation (2 responses); anaplastic carcinoma versus epithelioid hemangioendothelioma (1 response); and sarcoma (2 responses), clearly illustrating the problems posed in diagnosis by this variant of anaplastic thyroid carcinoma.[28] This variant is uncommon, and constituted 5.7% of 35 cases of anaplastic carcinoma in our files. Although the individual histologic features (spindle cells, sclerosis, and infarction) have been alluded to or illustrated in some series on anaplastic thyroid carcinoma,[1,6,7] this variant (with all the features occurring together as a predominant pattern) has not been singled out to emphasize the problem in diagnosis.

The histologic mimicry of Riedel's thyroiditis is due to the low cellularity, presence of spindle cells resembling fibroblasts or myofibroblasts, the general lack of obvious nuclear anaplasia, and the sprinkling of lymphocytes. The features that favor a diagnosis of paucicellular variant of anaplastic thyroid carcinoma over Riedel's thyroiditis include: (1) coagulative necrosis, distinguishable from sclerohyaline fibrosis by the presence of "ghost" blood vessels and total absence of stainable nuclei, and the prominence of infarction is probably attributable to obliteration of blood vessels by tumor; (2) presence of more cellular areas associated with nuclear atypia (although often subtle) and mitosis in some foci, especially at the periphery; (3) plump spindle cells plugging large muscular vessels instead of phlebitis caused by lymphoplasmacytic infiltrate around the vessel wall as in cases of Riedel's thyroiditis;[6,29] this is a well-recognized phenomenon in anaplastic thyroid carcinoma;[1,2,7] (4) discrete interface of the lesion with the surrounding tissue, favoring a neoplastic rather than reactive process; and (5) lymph node involvement, if present. Immunohistochemical

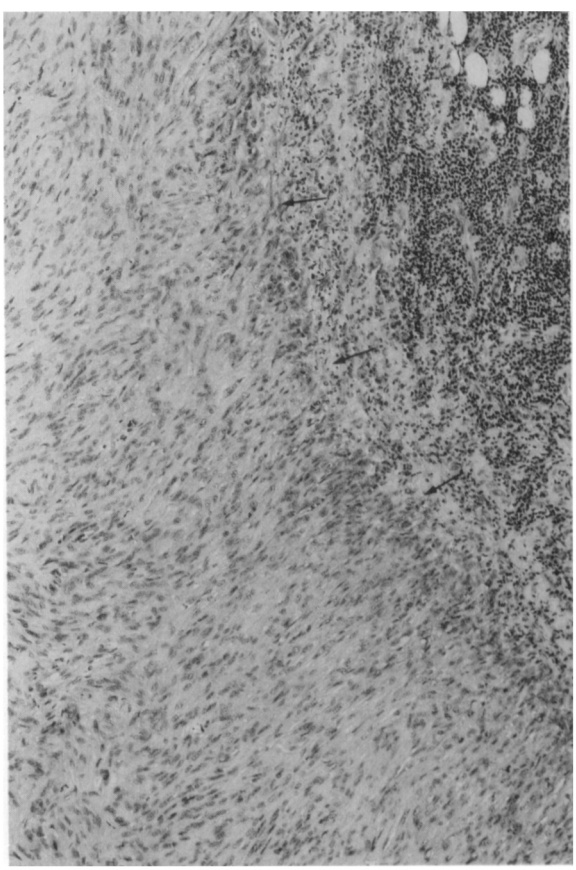

FIG. 6. More cellular growth in focal areas of the tumor. The fascicular growth and the discrete invading front (arrows) favor the interpretation of a neoplastic rather than inflammatory process (case 2).

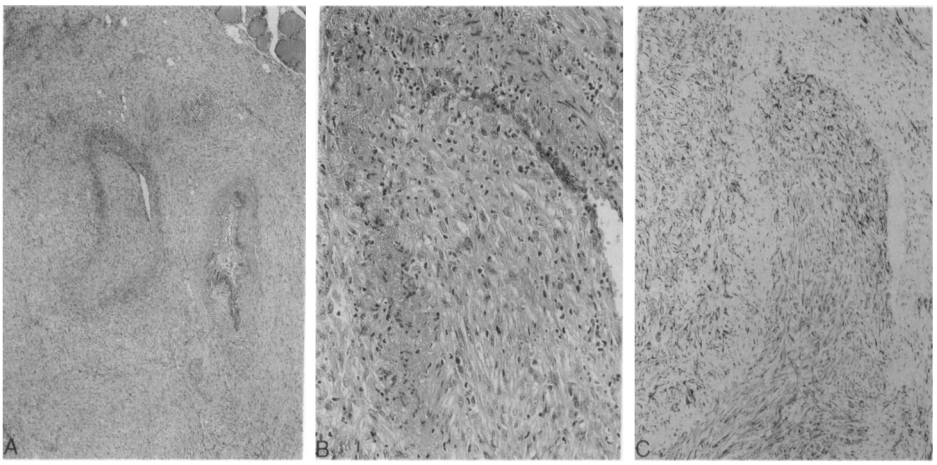

FIG. 7. The tumor shows obliteration of blood vessels, which is a clue to the diagnosis of anaplastic carcinoma (case 2). A, The blood vessel in the center shows luminal obliteration by the spindle cells (neoplastic proliferation). B, Higher magnification showing the presence of definite, albeit mild to moderate, nuclear atypia. C, A corresponding field shows that the tumor cells within and outside the blood vessel are immunoreactive for cytokeratin.

studies may support the diagnosis of carcinoma over fibroblastic reaction of Riedel's thyroiditis if staining for cytokeratin is positive (a phenomenon reported in 50% to 100% of anaplastic thyroid carcinoma),[1,3,8] although caution is required in interpretation because myofibroblasts can show sporadic staining for cytokeratin. Judging from the clinical features and aggressive behavior, the paucicellular variant of anaplastic thyroid carcinoma appears to be merely a morphologic variant with no prognostic implication. However, the importance of its recognition lies in its potential for being mistaken for Riedel's thyroiditis. Of interest, this tumor shows many histologic similarities with inflammatory sarcomatoid carcinoma of the lung, a neoplasm recently described by Wick and colleagues.[30] Both are sarcomatoid carcinomas with deceptively bland neoplastic cells, and thus mimic an inflammatory process.

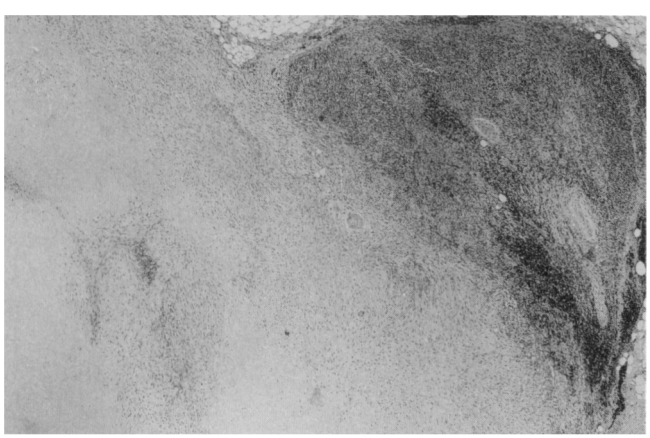

FIG. 8. Lymph node from case 2. It is largely replaced by hypocellular tumor similar to that seen in the thyroid gland. Residual lymphoid tissue is seen in the upper field.

REFERENCES

1. Carcangiu ML, Steeper T, Zampi G, Rosai J. Anaplastic thyroid carcinoma: A study of 70 cases. *Am J Clin Pathol* 1985;83:135–158.
2. Rosai J, Saxem EA, Woolner L. Undifferentiated and poorly differentiated carcinoma. *Semin Diagn Pathol* 1985;2:123–126.
3. LiVolsi VA, Brooks JJ, Arendash-Durand B. Anaplastic thyroid tumors, immunohistochemistry. *Am J Clin Pathol* 1987;87:434–442.
4. Nel CJC, van Heerden JA, Goellner JR. Anaplastic carcinoma of the thyroid: A clinicopathologic study of 82 cases. *Mayo Clin Proc* 1985;60:51–58.
5. Aldinger KA, Samaan NA, Ibanez M, Hill CS. Anaplastic carcinoma of the thyroid: A review of 84 cases of spindle cell and giant cell carcinoma of the thyroid. *Cancer* 1978;41:2267–2275.
6. LiVolsi VA. Surgical Pathology of the Thyroid. Major Problems in Pathology. vol 22. Philadelphia: WB Saunders, 1990.
7. Rosai J, Carcangiu ML, DeLellis RA. Tumors of the Thyroid Gland. Atlas of Tumor Pathology, 3rd series, Fascicle 5. Washington DC: Armed Forces Institute of Pathology, 1992.
8. Venkatesh YSS, Ordonez NG, Schultz PN, et al. Anaplastic carcinoma of the thyroid: A clinicopathologic study of 121 cases. *Cancer* 1990;66:321–330.
9. Riedel BMCL. Die chronische, zur Bildung eisenharter Tumoren fuhrende Entzundung der Schilddruse. *Verh Dtsch Ges Chir* 1896;25:101–105.
10. Riedel BMCL. Vorstellung eines Kranken mit chronischer Strumitis. *Verh Dtsch Ges Chir* 1897;26:127–129.
11. Ewing J. Neoplastic Diseases. ed 2. Philadelphia: WB Saunders, 1928, pp 908–909.
12. Merrington WR. Chronic thyroiditis: A case showing features of both Riedel's and Hashimoto's thyroiditis. *Br J Surg* 1948;35:423–426.
13. Rose E, Royster HP. Invasive fibrous thyroiditis (Riedel's struma). *JAMA* 1961;176:224–226.
14. Raphael HA, Beahrs DH, Woolner LB. Scholz DA. Riedel's struma associated with fibrous mediastinitis: Report of a case. *Mayo Clin Proc* 1966;41:375–382.
15. Nielson HK. Multifocal idiopathic fibrosclerosis: Two cases with simultaneous occurrence of retroperitoneal fibrosis and Riedel's thyroiditis. *Acta Med Scand* 1980;208:119–123.
16. Rao CR, Ferguson GC, Kyle VN. Retroperitoneal fibrosis associated with Riedel's struma. *Can Med Assoc J* 1973;108:1019–1021.
17. Turner-Warwich R, Nabarro JD, Doniach D. Riedel's thyroiditis and retroperitoneal fibrosis. *Proc R Soc Med* 1966;59:596–598.

18. deBoer WA, van Coevorden F, Wiersinga WM. A rare case of Riedel's thyroiditis, 6 years after retroperitoneal fibrosis: Two diseases with one pathogenesis? *Neth J Med* 1992;40:190–196.
19. Best TB, Munro RE, Burwell S, Volpe R. Riedel's thyroiditis associated with Hashimoto's thyroiditis, hypoparathyroidism, and retroperitoneal fibrosis. *J Endocrinol Invest* 1991;14:767–772.
20. Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO. Sclerosing cholangitis: Its possible association with Riedel's struma and fibrous retroperitonitis. *N Engl J Med* 1963;269:8–12.
21. Gleeson MH, Taylor S. Dowling RH. Multifocal fibrosclerosis. *Proc R Soc Med* 1970;63:1309–1311.
22. Amorosa LF, Shear K, Spiera H. Multifocal fibrosis involving the thyroid, face, and orbits. *Arch Intern Med* 1976;136:221–223.
23. Arnott EJ, Greaves DP. Orbital involvement in Riedel's thyroiditis. *Br J Ophthal* 1965;49:1–5.
24. Schneider RJ. Orbital involvement in Riedel's struma. *Can J Ophthalmol* 1976;11:87–90.
25. Sclare G, Luxton RW. Fibrosis of the thyroid and lacrimal glands. *Br J Ophthalmol* 1967;51:173–177.
26. Wilmshurst P, Msom R, Gostelow B. Orbital pseudotumor and lacrimal involvement developing in a patient with Riedel's struma receiving steroids. *Clin Endocrinol (Oxf)* 1981;14:63–67.
27. Schwaegerle SM, Bauer TW, Esselstyn CB Jr. Riedel's thyroiditis. *Am J Clin Pathol* 1988;90:715–722.
28. Chan JKC, Tsang WYW. Endocrine malignancies that may mimic benign lesions. *Semin Diagn Pathol* 1995;12:45–63.
29. Woolner LB. McConahey WM, Beahrs OH. Invasive fibrous thyroiditis. *J Clin Endocrinol Metab* 1957;17:201–210.
30. Wick MR, Ritter JH, Nappi O. Inflammatory sarcomatoid carcinoma of the lung: Report of three cases and clinicopathologic comparison with inflammatory pseudotumors in adult patients. *Hum Pathol* 1995;26:1014–1021.

HOLOGIC®

First and Only FDA Cleared

Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager

Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System

Click or Scan
to discover more

genius™
DIGITAL DIAGNOSTICS