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# Epithelioid angiosarcoma of the thyroid

## Clinicopathological analysis of seven cases from non-Alpine areas

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**Abstract** Epithelioid angiosarcomas of the thyroid usually develop in people living in Alpine regions, and only rare cases arising in subjects living in nonmountainous areas have been reported. We describe the clinicopathological features of a series of seven cases collected from non-Alpine areas. All patients were adults. The tumours appeared as haemorrhagic, unencapsulated, sometimes cystic nodules. In two cases multinodularity was present. They were composed of large, epithelioid cells, which lined vascular-like spaces or were arranged in solid sheets. Intracytoplasmic lumina containing red blood cells were identified. Neoplastic cells were diffusely positive for factor VIII-related antigen, *Ulex europaeus* agglutinin, CD31 and keratin peptides. Ultrastructural studies were performed in four cases and showed features of endothelial differentiation. An average follow-up of 3.8 years disclosed that four patients died of disease after a median survival time of 5 months, whereas 3 patients are still alive with no evidence or residual disease 27, 32 and 66 months after thyroidectomy. The good prognosis in these patients appears to be related mainly to the absence of extraglandular tumour spread at the time of surgery.

**Key words** Thyroid · Angiosarcoma · Immunohistochemistry · Ultrastructure

## Introduction

Whether primary angiosarcoma (malignant haemangioendothelioma) of the thyroid gland exists as a distinct entity or is merely a vascular variant of anaplastic carcinoma has been a matter of debate for almost a century. Originally described by Swiss authors [9, 14] as a separate type of neoplasm of endothelial origin as early as 90 years ago, it was considered by American authors [15] to represent a morphological variant of undifferentiated carcinoma.

The immunohistochemical detection of factor VIII-related antigen (FVIII-RA) [17, 19, 24] and the ultrastructural identification of Weibel-Palade bodies [5, 6] confirmed the occurrence of endothelial differentiation in neoplastic cells, giving credit to the histogenetic theory postulated by Swiss authors. Eusebi et al. [6] demonstrated the coexpression of endothelial markers and cytokeratins in such thyroid tumours and christened them "epithelioid angiosarcomas", in order to stress their distinction from anaplastic carcinomas. The discussion has not been settled, however, as shown by the development of theories postulating the coexistence of a bidirectional (epithelial and endothelial) differentiation in the same neoplasm [4, 16, 25].

Since this tumour has been mainly, although not exclusively, observed in people living in mountainous regions, such as the European Alps, reported series have stressed the geographic confinement and the "Alpine predilection" of this pathology [5, 8], underlining its link with iodine-deficient goitre as a predisposing factor [8]. Only sporadic cases have been described from nonmountainous or coastal areas [2, 3, 6, 18, 23].

The aim of this study was to review the clinical and pathologic findings in a series of seven cases of epithelioid angiosarcoma of the thyroid that had arisen in subjects living in non-Alpine regions. Cases were studied with immunohistochemical and ultrastructural methods. Follow-up was available in all patients.

## Materials and methods

Five thyroid tumours were retrieved from the files of the Institute of Pathological Anatomy of the University of Modena during the years 1990–1994. Two cases were obtained from the consultation files of one of us (V.E.). Clinical history and follow-up informa-

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**Table 1** List of antibodies used in this study. Antibodies were directed against the following antigens (*P* polyclonal, *M* monoclonal)

| | P/M | Clone | Source |
|---|---|---|---|
| Factor VIII-related antigen | P | – | Dako |
| CD31 | M | EPOQ | Bioptica |
| CD34 | M | QBN10 | Ylem |
| VIM | M | V9 | Dako |
| Keratin peptides 8, 18, 19 | M | CAM 5.2 | Becton-Dickinson |
| Acidic (low molecular weight) keratin peptides | M | AE1 | Biomeda |
| Basic (high molecular weight) keratin peptides | M | AE3 | Biomeda |
| EMA | M | E29 | Dako |
| Thyroglobulin | P | – | Ortho |
| Calcitonin | P | – | Ortho |

tion was available in all patients. None of these cases had been previously reported.

Thyroidectomy specimens had been fixed in 4% formaldehyde and embedded in paraplast. The following numbers of blocks were available in five cases: 2 (case 1), 5 (case 2), 3 (case 3), 4 (case 4), 4 (case 5). In two cases (6 and 7) only a limited number of unstained slides were available. Sections were stained with haematoxylin and eosin (HE) and PAS.

Immunohistochemistry was performed in all cases using the avidin–biotin-amplification system and a panel of commercially available antibodies directed against the antigens listed in Table 1. Staining with the lectin *Ulex europaeus* agglutinin 1 (UEA-1, Vector) was also performed. Endogenous peroxidase activity was blocked by $H_2O_2$-methanol treatment. Microwave pretreatment was performed against CD31, CD34, vimentin, AE1 and AE3, using a household microwave oven for 10 min (2×5 min) at 600 W. The extent of immunohistochemical staining in each case was semiquantitatively evaluated by the following grading system: –, no reaction; +, less than 10% of positive cells; ++, more than 10% of positive cells.

Ultrastructural studies were carried out in four cases using formalin-fixed tissue. The material was post-fixed in $OsO_4$, dehydrated and embedded in epoxy resin. Semithin sections were cut to ensure representative sampling. Ultrathin sections were stained with uranyl acetate and lead citrate and viewed with a Zeiss EM 109 electron microscope.

## Case histories

The clinical features are summarized in Table 2. Five patients were from areas located in northern Italy. Four of them (cases 1, 2, 3, 4) were from the province of Modena and one (case 7), from nearby Reggio Emilia. Four patients (cases 2, 3, 4, 7) lived in flatland (Po valley), whereas case 1 lived in a hilly pre-Appenine goitrogenous area (600 m above sea level). One patient came from coastal Sicily (case 5) and one from The Netherlands (case 6).

Cases came to medical attention either because of a rapidly enlarging nodule in the neck, or because of dysphagia and acute dyspnoea (case 5). Case 2 underwent surgery because of a thyroid cyst, which had recurred several times after aspiration during the last year. Extracapsular extension with neoplastic infiltration of neck muscles and/or distant metastases was present in three patients (cases 2, 5, 7), unstated in one (case 6) and absent in three (cases 1, 3, 4).

Total thyroidectomy was performed in all patients and was followed by radiotherapy in three of them (Table 2). Three patients are still alive with no evidence of recurring disease after a follow-up period of 66, 32 and 27 months, whereas the other four (cases 2, 5, 6, 7) died of their disease 5, 4, 9 and 5 months, respectively, after thyroidectomy. Autopsy was not performed in any of the cases.

In order to highlight possible clinicopathological factors that might be related to survival, clinical records and histological sections were reviewed to investigate the importance of the following variables in survivors and nonsurvivors: (1) size of the lesions; (2) presence or absence of extraglandular tumour spread at the time of surgery, both the local extension of the tumour beyond the boundaries of the thyroid capsule and the occurrence of distant site metastases being considered; (3) multinodularity; (4) amount of tumour necrosis; (5) extent of fibrosis; (6) mitotic activity (×10 HPF); (7) degree of lymphoplasmacytic infiltration; and (8) extent of calcification within tumours.

Statistical analysis (chi-square test) showed no significant differences ($P>0.05$) in all the variables considered. However, it is worth underlining that all patients with intrathyroidal tumours are still alive after a follow-up period ranging from 27 to 66 months, whereas the patients with extraglandular tumours died of the disease.

## Pathologic findings

The tumours were red-brown, widely haemorrhagic, unencapsulated masses ranging in size from 2.5 to 9 cm (mean: 4.84 cm) in maximum diameter (Table 2). Grey-

**Table 2** Clinical features of seven cases of epithelioid angiosarcoma of the thyroid (*ANED* alive, no evidence of disease; *DOD* dead of disease; *TT* total thyroidectomy; *RT* radiotherapy)

| Case no. | Sex/age (years) | Site and size of tumour | Extrathyroid extension | Treatment | Follow-up |
|---|---|---|---|---|---|
| 1 | F/84 | Left lobe (3 cm) | No | TT | ANED (66 months) |
| 2 | F/60 | Left lobe (9×3 cm) | Yes (neck mucles) | TT+RT | DOD (5 months) (local recurrence) |
| 3 | F/69 | Left lobe(5×3.5 cm) | No | TT | ANED (32 months) |
| 4 | F/60 | Left lobe (2.2×2.5 cm) + 2 small (1 cm) nodules in right lobe | No | TT | ANED (27 months) |
| 5 | F/84 | Right lobe 2 nodules (3 cm each) | Yes (neck muscles, trachea, mediastinum) | TT | DOD (4 months) (lung metastases) |
| 6 | M/62 | Right lobe (6 cm) | Not stated | TT+RT | DOD (9 months) (lung, brain ? metastases) |
| 7 | F/50 | Right lobe (5.4 cm) | Yes (neck muscles) | TT+RT | DOD (5 months) (lung, pleura metastases) |

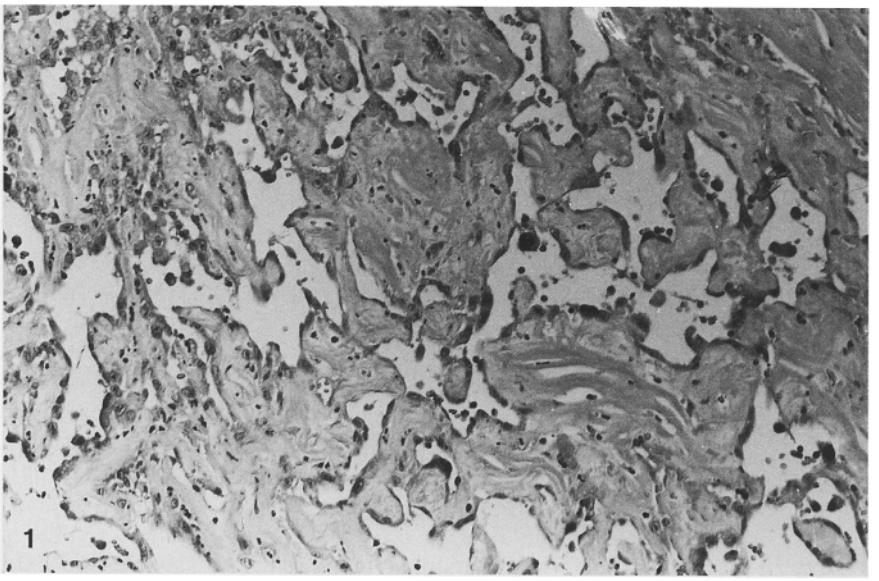


**Fig. 1** A complex network of small vascular-like spaces was observed in all cases (case 2). HE, ×25

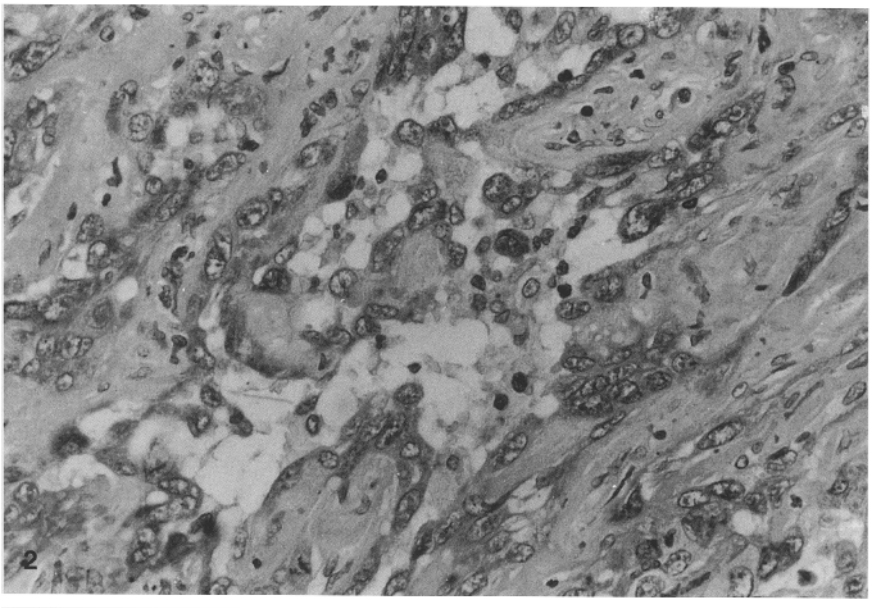


**Fig. 2** Dilated channels lined by plump neoplastic cells and filled with erythrocytes (case 3). HE, ×125

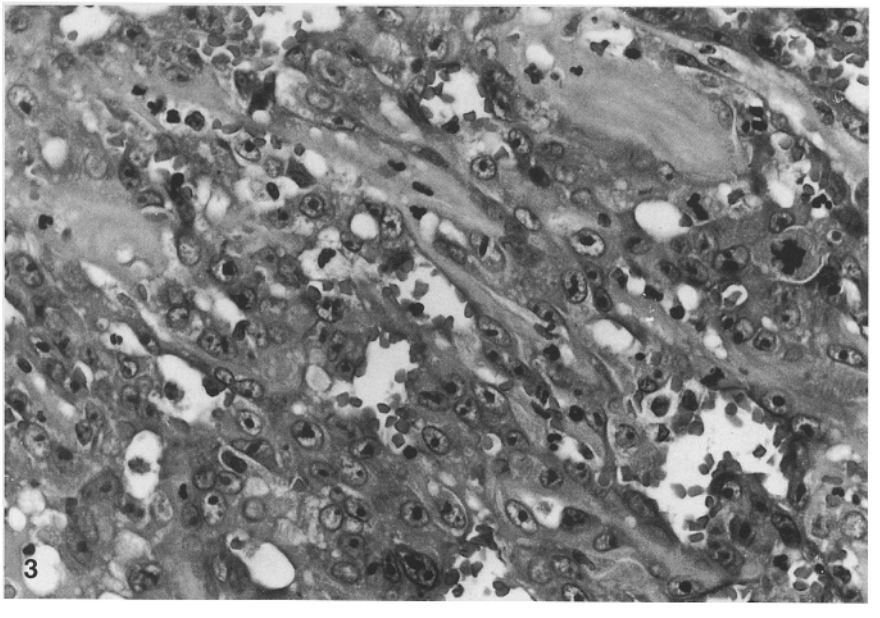


**Fig. 3** Neoplastic cells exhibited epithelioid features, showing abundant cytoplasm and large, vescicular nuclei with prominent nucleoli (case 5). HE, ×250

**Table 3** Summary of immunohistochemical results (*FVIII* factor VIII-related antigen, *UEA-1 Ulex europaeus* agglutinin 1, *EMA* epithelial membrane antigen, *TG* thyroglobulin, *CALC* calcitonin; – absence of staining, + staining in <10% of neoplastic cells, ++ positive reaction in >10% of neoplastic cells)

| Case no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| FVIII | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| UEA-1 | ++ | ++ | ++ | ++ | ++ | + | + |
| CD31 | ++ | + | ++ | ++ | ++ | ++ | + |
| CD34 | ++ | – | – | ++ | ++ | – | + |
| VIM | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| CAM 5.2 | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| AE1 | – | ++ | ++ | – | ++ | + | ++ |
| AE3 | – | + | + | – | – | – | – |
| EMA | ++ | ++ | ++ | + | ++ | + | – |
| TG | – | – | – | – | – | – | – |
| CALC | – | – | – | – | – | – | – |

yellowish necrotic zones were frequent. Cystic areas with thick, partly calcified walls were observed in two cases (2 and 4), whereas in case 1 the tumour was a well-delimited, whitish, extensively fibrotic nodule with focal necrotic and haemorrhagic areas. Multiple tumour nodules were present in two cases (4 and 5), occupying one or both thyroid lobes.

The light microscopic appearance was similar in all cases. Tumours were poorly circumscribed and exhibited extensive foci of necrosis and haemorrhage. Vascular-like spaces lined with flattened or plump neoplastic cells were present in all cases, accounting for approximately 20–50% of the histological section in different tumours. These consisted mainly of an intricate network of small capillary-sized lumina, in some areas enlarging to form dilated, ramifying channels of irregular shape, filled with erythrocytes and epithelioid neoplastic cells (Figs. 1, 2). Intravascular papillary fronds were occasionally present. In other areas, tumours featured a solid pattern of growth with cells arranged in sheets or nests, separated by little or no intervening stroma. Intracytoplasmic lumina, often containing identifiable red blood cells, were seen.

Neoplastic cells were large and featured abundant, sharply demarcated, eosinophilic cytoplasm and round or oval, large, vesicular nuclei containing one or more prominent nucleoli (Fig. 3). Pleomorphism was not notable, but mitotic figures were numerous and often irregular.

Haemosiderin deposits, and also microcalcifications, were common. Extensive calcification was observed in case 4. Case 1 featured widespread acellular sclerohyalinosis intermixed with necrotic debris in the central parts of the tumour mass, the viable neoplastic tissue being confined at the periphery of the nodule. In case 7, numerous small, PAS-positive, diastase-resistant hyalin globules reminiscent of those usually found in Kaposi's sarcoma were observed (Fig. 4).

Nonneoplastic thyroid showed long-standing multinodular goitre with various degrees of regressive changes, such as colloid cyst formation, haemorrhage, fibrohyalinosis and calcifications.

The immunohistochemical features are summarized in Table 3. A diffuse reactivity for vimentin, FVIII-RA and *Ulex europaeus* agglutinin 1 was detected in neoplastic cells of all cases. Staining for CD31 (Fig. 5) was observed in seven of the seven tumours, whereas the reaction for CD34 was positive in four cases. Epithelial markers were found to be expressed in all tumours. In particular, reactivity for CAM 5.2 (Fig. 6) was observed in all seven cases (extensively in four, focally in three), whereas acidic keratin peptides (AE1) were detected in five of the seven cases and basic keratin peptides (AE3) in two of the seven (focally). Staining for EMA was positive in six tumours. Thyroglobulin and calcitonin exhibited a negative reaction in all cases.

Ultrastructural examination showed neoplastic cells with large, round to oval, at times indented, nuclei exhibiting prominent nucleoli and marginated chromatin. Neoplastic cells frequently lined erythrocyte-containing spaces and exhibited abundant cytoplasm with micropinocytotic vescicles (Fig. 7). Single membrane-bound, rod-shaped cytoplasmic structures, reminiscent of Weibel-Palade bodies, were observed in neoplastic cells of all cases (Fig. 7, inset). They approached 150 nm in diameter and showed an inner parallel tubular array. Occasional intracytoplasmic lumina were seen. Intracytoplasmic aggregates of intermediate filaments consistent with keratins were clearly visible in case 3.

## Discussion

Originally thought to be confined to Alpine regions, such as Austria and Switzerland [5, 8], where it accounted for 4.3% of all thyroid tumours during the period 1962–1973 [8], thyroid angiosarcoma has been reported sporadically in nonmountainous areas, such as Hong Kong [3], northern France [18] and the United Kingdom [2]. Cases have also been described from northern nonmountainous Italy and coastal areas of the U.S. [6].

In the series here reported, the previously emphasized Alpine predilection of thyroid angiosarcoma is lacking. Two cases were from coastal regions, whereas five were collected during a 5-year period from the Modena area and nearby Reggio Emilia, situated in the Emilia-Romagna region in northern Italy. For unknown reasons, the diagnosis of thyroid angiosarcoma in this area is more common than it is in other parts of the world (Alpine regions excluded). Although no statistical data can be supplied to support this statement, it is worth mentioning that a rough estimate of the number of malignant thyroid tumours (excluding malignant lymphomas) diagnosed at the Institute of Pathological Anatomy of Modena during the quinquennium 1990–1994 showed that the percentage of angiosarcomas was approximately 2.3%. This finding appears to be more than would be expected by chance and deserves further investigation. Parenthetically, three of the four thyroid angiosarcomas reported by Eusebi et al. [6] were from neighbouring provinces of the same Italian region. This challenges the be-

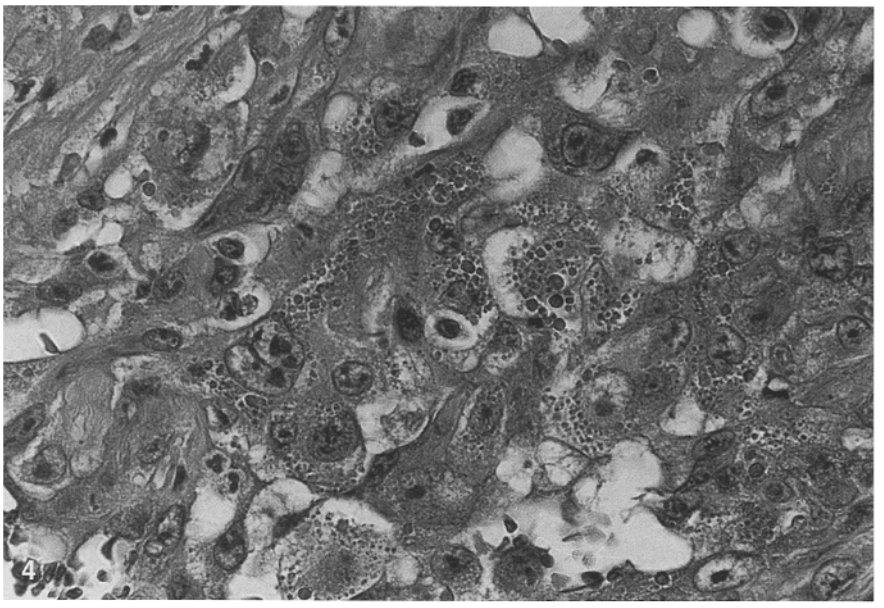


**Fig. 4** PAS-positive, intracytoplasmic hyalin globules were observed in this case (case 7). PAS, ×400

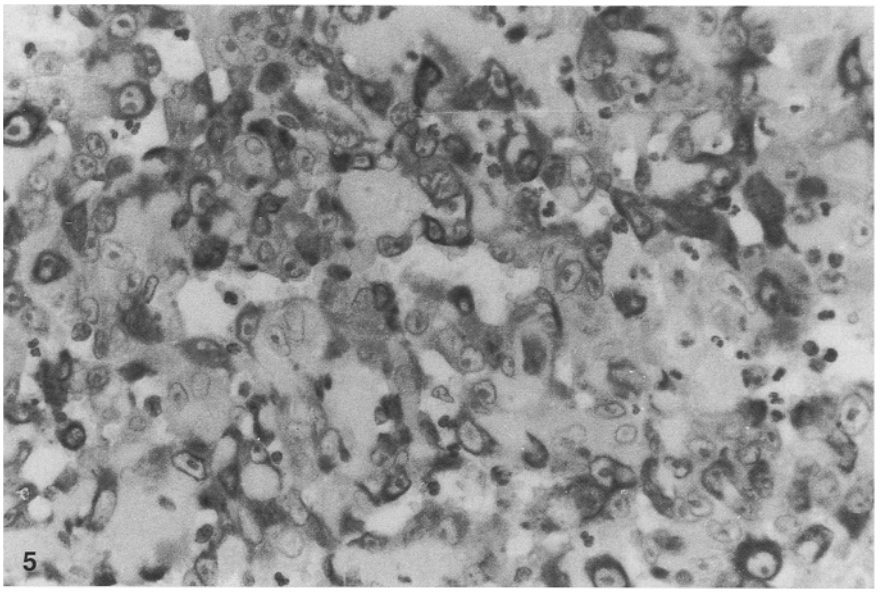


**Fig. 5** Positive reaction for CD31 in neoplastic cells (case 3). ABC method, ×250

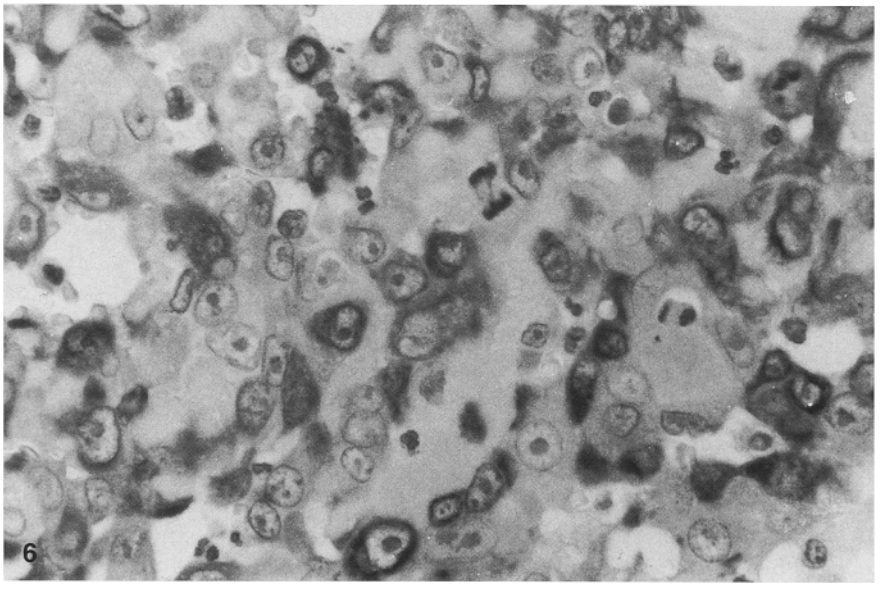


**Fig. 6** Cytoplasmic reactivity for low-molecular-weight keratin peptides (MoAb CAM 5.2; case 5). ABC method, ×300

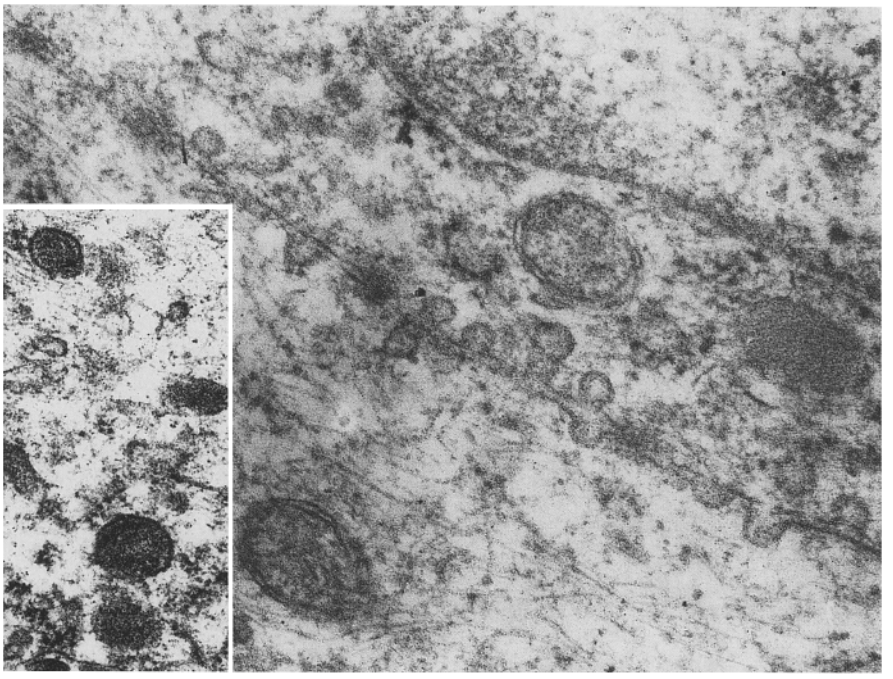

**Fig. 7** Micropinocytotic vescicles at the surface of a neoplastic cell (case 3). ×30,000. *Inset*: round structures with microtubular array, reminiscent of Weibel-Palade bodies. ×42,000

lief that iodine-deficient goitre is the only predisposing factor in the development of thyroid angiosarcoma, suggesting that other unknown (probably environmental) agents may be involved in its pathogenesis.

The morphological detection of anastomosing, capillary-sized or dilated spaces containing erythrocytes and the occurrence of an endothelial phenotype in neoplastic cells, as seen from the immunoreactivity with endothelial markers and from the ultrastructural features, all provide evidence of vascular differentiation in these thyroid tumours and allow their distinction from anaplastic carcinomas. At least three endothelial markers (FVIII-RA, UEA-1 and CD31) were found to be consistently expressed by neoplastic cells from all cases. The reaction was diffuse in the majority of tumours, being focal only in isolated cases.

Positivity for keratin peptides 8, 18, 19, as evidenced by the use of monoclonal antibody CAM 5.2, was detected in all tumours. Five of the seven cases stained for acidic keratin peptides (MoAb AE1), whereas only two of these five were positive for basic keratin peptides (MoAb AE3). The finding of immunoreactivity for cytokeratins in angiosarcomas is not surprising. Already described in a variety of bone and soft tissue sarcomas [20] and in benign and malignant epithelioid endothelial neoplasms of different sites [7], it has also been reported in epithelioid angiosarcomas of the thyroid [6, 13]. Its occurrence has been related either to atavism [1], as epitomized by the demonstration of keratin peptides in embryonal endothelial cells [10], or alternatively to neoplastic anarchy [1], a consequence of the alterations induced in the ordered genomic structure by transforming factors [11]. However, scepticism about the real presence of cytokeratins in soft tissue tumours has been expressed by some authors [21, 22], who consider its apparent immunohistochemical detection in mesenchymal neoplasias the consequence of spurious results [21].

Evidence of endothelial differentiation in neoplastic cells can also be derived from ultrastructural investigation, as seen in the four cases studied that showed features consistent with vascular differentiation, such as the occurrence of pinocytotic vescicles and of single membrane-bound, cylindrical structures identified by their dimensions and microtubular array as Weibel-Palade bodies. The occurrence of Weibel-Palade bodies in isolated cases of malignant haemangioendothelioma of the thyroid has been reported in the literature [3, 5, 19, 23]. Incidentally, the case reported by Tanda et al. [23] subsequently showed heavy staining for low-molecular-weight keratins (V.E., personal communication).

Thyroid angiosarcomas, like anaplastic carcinomas, are high-grade malignancies and, as such, are usually associated with a dismal prognosis. At diagnosis, tumours are often found already to have invaded the soft tissues of the neck, reducing the chance of radical removal. In most series, patients have succumbed to tumour disease after less than 6 months [5, 12]. Only isolated examples of patients surviving as long as 2 [6], 3 [13] or even 4½ years [12] are documented.

Follow-up data in this study suggest that early diagnosis might have a favourable influence on survival. At surgery, an intraglandular mass was found in each of three patients, while infiltration of extracapsular stuctures and distant metastasis were already present in three. All three patients with intrathyroidal tumours are still alive after follow-up periods ranging from 27 to 66 months, even if no further treatment was given after total thyroidectomy. For one patient the local extension of the tumour was not stated in the surgical records.

The three patients in whom tumours had already invaded extraglandular structures at the time of surgery died in spite of intensive therapy. Their median survival time was 5 months. The main reasons for the death of these patients were rapid local tumour growth with infiltration of neck muscles and trachea and occurrence of multiple distant lung and pleural metastases.

These findings suggest that the outcome for patients with thyroid angiosarcomas is not necessarily as poor as has been reported previously. In the majority of cases, the prognosis depends mainly on the stage at which the patient undergoes treatment, the limiting factor being the intraglandular location of the tumour. Early diagnosis at a stage at which the sarcoma has not yet spread beyond the boundaries of the thyroid capsule is therefore paramount, to ensure the possibility of radical surgical removal and improve the prognosis of such patients.

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## References

1. Battifora H (1990) Expression of keratins by endothelial cells: atavism or anarchy? (editorial). Ultrastruct Pathol 14:III–V
2. Beer TW (1992) Malignant thyroid haemangioendothelioma in a non-endemic goitrous region, with immunohistochemical evidence of a vascular origin. Histopathology 20:539–541
3. Chan YF, Ma L, Boey JH, Yeung HY (1986) Angiosarcoma of the thyroid. An immunohistochemical and ultrastructural study of a case in a Chinese patient. Cancer 57:2381–2388
4. Eckert F, Schmid U, Gloor F, Hedinger C (1986) Evidence of vascular differentiation in anaplastic tumours of the thyroid: an immunohistological study. Virchows Arch [A] 410:203–215
5. Egloff B (1983) The hemangioendothelioma of the thyroid. Virchows Arch [A] 400:119–142
6. Eusebi V, Carcangiu ML, Dina R, Rosai J (1990) Keratin-positive epithelioid angiosarcoma of thyroid. A report of four cases. Am J Surg Pathol 14:737–747
7. Gray MH, Rosenberg AE, Dickersin GR, Bhan AK (1990) Cytokeratin expression in epithelioid vascular neoplasms. Hum Pathol 21:212–217
8. Hedinger C (1981) Geographic pathology of thyroid diseases. Pathol Res Pract 171:285–292
9. Hedinger E (1909) Zur Lehre der Struma Sarcomatosa. I. Die Blutgefaeßendotheliome der Struma. Frankfurt Z Pathol 3: 487–540
10. Jahn L, Fouquet B, Rohe K, et al (1987) Cytokeratins in certain endothelial and smooth muscle cells of two taxonomically distant vertebrate species, *Xenopus laevis* and man. Differentiation 36:234–254
11. Knapp AC, Franke WW (1989) Spontaneous losses of control of cytokeratin gene expression in transformed, non-epithelial cells occurring at different levels of regulation. Cell 50:67–69
12. Ladurner D, Toetsch M, Luze T, Bangerl I, Sanbichler P, Schmid KW (1990) Das maligne Haemangioendotheliom der Schilddrüse. Pathologie, Klinik und Prognose. Wien Klin Wochenschr 102:256–259
13. Lamovec J, Zidar A, Zidanik B (1994) Epithelioid angiosarcoma of the thyroid gland. Report of two cases. Arch Pathol Lab Med 118:642–646
14. Limacher F (1898) Ueber Blutgefaeßendotheliome der Struma mit einem Anhang ueber Knochenmetastasen bei Struma maligna. In: Virchow R (ed) Beiträge zur Geschwulstlehre. Arch Pathol Anat Physiol Klin Med [Suppl] 151:113–150
15. Meissner WA, Warren S (1969) Tumors of the thyroid gland. (Atlas of tumor pathology, 2nd ser, fasc 4) Armed Forces Institute of Pathology, Washington, DC
16. Mills SE, Gaffey MJ, Watts JC, Swanson PE, Wick MR, LiVolsi VA, Nappi O, Weiss LM (1994) Angiomatoid carcinoma and "angiosarcoma" of the thyroid gland. A spectrum of endothelial differentiation. Am J Clin Pathol 102:322–330
17. Pfaltz M, Hedinger C, Saremaslani P, Egloff B (1983) Malignant hemangioendothelioma of the thyroid and factor VIII-related antigen. Virchows Arch [A] 401:177–184
18. Pusel J, Rodier JF, Auge B, Janser JC (1993) Hémangioendothéliome malin de la thyroïde. Etude anatomoclinique d'un cas. Ann Pathol 13:253–255
19. Ruchti C, Gerber HA, Schaffner T (1984) Factor VIII-related antigen in malignant hemangioendothelioma of the thyroid: additional evidence for the endothelial origin of this tumor. Am J Clin Pathol 82:474–480
20. Schaafsma HE, Ramaekers FCS (1994) Cytokeratin subtyping in normal and neoplastic epithelia; basic principles and diagnostic application. Pathol Annu 29:21–62
21. Sirgi KE, Wick MR, Swanson PE (1993) B72.3 and CD34 immunoreactivity in malignant epithelioid soft tissue tumors. Adjuncts in the recognition of endothelial neoplasms. Am J Surg Pathol 17:179–185
22. Swanson PE (1991) Heffalumps, jagulars and cheshire cats. A commentary on cytokeratins and soft tissue sarcomas. Am J Clin Pathol [Suppl] 95:S2–S7
23. Tanda F, Massarelli G, Bosincu L, Cossu A (1988) Angiosarcoma of the thyroid: a light, electron microscopic and histoimmunological study. Hum Pathol 19:742–745
24. Toetsch M, Dobler G, Feichtinger H, Sandbichler P, Ladurner D, Schmid KW (1990) Malignant hemangioendothelioma of the thyroid. Its immunohistochemical discrimination from undifferentiated thyroid carcinoma. Am J Surg Pathol 14:69–74
25. Vollenweider I, Hedinger C, Saremaslani P, Pfaltz M (1989) Malignant hemangioendothelioma of the thyroid, immunohistochemical evidence of heterogeneity. Pathol Res Pract 184: 376–381