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Case report

Diffuse sclerosing variant of papillary thyroid carcinoma

S-100 protein immunocytochemistry and prognosis*

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Summary. The recently published second edition of the WHO classification of thyroid tumours describes the diffuse sclerosing papillary carcinoma (DSPC) as a specific variant of papillary thyroid cancer (PC). Besides several histological hallmarks, this rare tumour is characterized by its occurrence in young individuals and is thought to have a less favourable prognosis than PC in general. The observations on two examples of this tumour presented herein, however, are at variance at this assumption. The neoplasms occurred in a 10 year old girl and a 34 year old woman. Each time, diffuse involvement of both thyroid lobes and bilateral cervical lymphadenopathy were seen. In one case, the carcinoma extended into the cervical soft tissue. Follow-up disclosed both patients to be without evidence of disease 2 and 13 years, respectively, after thyroid surgery. Immunocytochemically, both thyroid primaries as well as 7 other cases of DSPC reported in the literature showed dense accumulations of S-100 protein positive dendritic/Langerhans cells. Such infiltrations have been demonstrated to be correlated with a benign clinical course of PC. It is thus suggested that DSPC behaves similarly or even less aggressively than PC in general, at least if prominent Langerhans cell infiltration is present.

Key words: Papillary thyroid carcinoma – Diffuse sclerosing variant – S-100 protein – Prognosis – Langerhans cells

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Introduction

We recently described the detection of S-100 protein positive Langerhans cell infiltrates in tumour tissue as a highly effective means of assessing the prognosis of patients with papillary thyroid carcinoma (Schröder et al. 1988). Irrespective of other morphological and clinical features, marked infiltration of such cells was correlated with a benign course, whereas slight infiltration or absence of the cells were associated with a poor prognosis. An objection was raised by Gómez-Morales et al. (1989) that they – like Chan et al. (1987) in their previous study of three such tumours – had observed dense Langerhans cell accumulations in four cases of a diffuse sclerosing variant of papillary cancer (DSPC). This type of neoplasm is said to have a less favourable prognosis than papillary thyroid carcinoma in general (Vickery et al. 1985) yet definite conclusions on a possibly more aggressive course have so far not been possible (Chan et al. 1987).

Gómez-Morales and co-workers failed to provide any clinical information on their four tumour cases, while the follow-up of the three patients reported by Chan et al. (1987) is too short for any meaningful conclusion. Hence, we searched for examples of this specific tumour variant in the surgical pathology files of the University Hospital Hamburg-Eppendorf (UKE) and the General Hospital Hamburg-Harburg (AKH) in order to determine their immunocytochemical pattern with respect to its prognostic significance.

Case reports

Between 1963 and 1988, 256 papillary thyroid carcinomas were seen at the Institute of Pathology, UKE. Among these, we

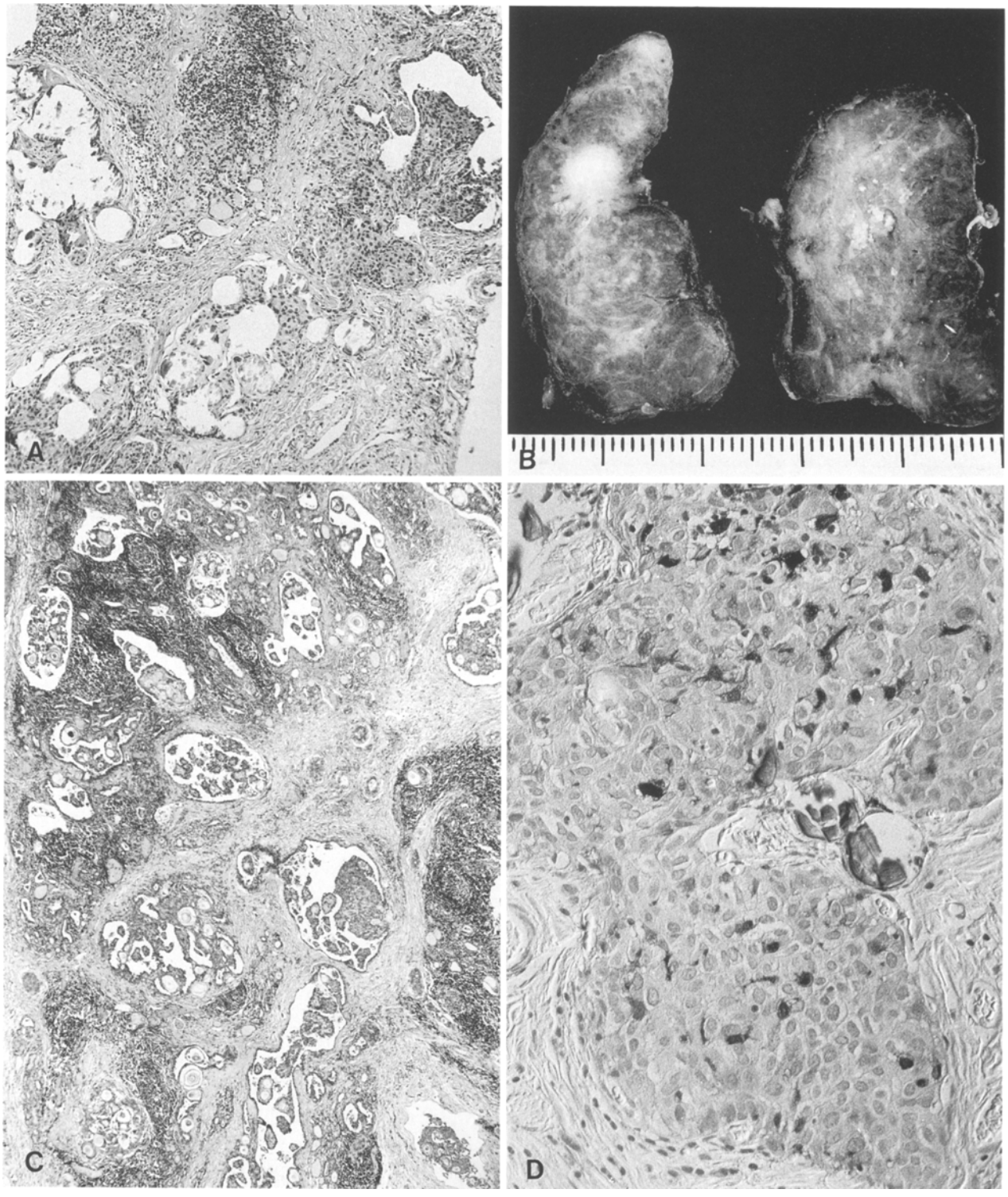

Fig. 1. (Case 1). **A** Histology of thyroid needle biopsy showing dense sclerosis, marked lymphocytic infiltration and numerous psammoma bodies (H&E ×66). **B** Gross view of thyroidectomy specimen. Fine streaking is to be seen on the cut surfaces of both lobes. Note white granular appearing compact tumour mass within the right lobe (on the left side of the illustration). **C** Low power magnification showing widespread dense fibrous stroma, scattered islands of PC and irregular zones of lymphocytic infiltration (H&E ×30). **D** Numerous LCs extending characteristic dendritic processes to be seen within solid epithelial islands (immuncytochemistry for S-100 protein ×200)

found one case of DSPC (case 1). This tumour constituted tissue referred to one of the authors as consultation material. The patient was a 10 year old girl whose only complaint was a painless right-preponderant swelling of the anterior portion of the neck, which had become progressively larger during the last 5 weeks prior to admission. Laboratory tests were suggestive of compensated hypothyroidism (elevation of TSH, total T4 decreased, T3 slightly increased). With regard to positive anti-thyroglobulin and anti-thyroid microsomal autoantibodies, a tentative diagnosis of Hashimoto's thyroiditis was made. In order to confirm this diagnosis, thyroid needle biopsy was performed, which however resulted in the finding of papillary thyroid carcinoma as illustrated in Fig. 1 a. Subsequently, total thyroidectomy and resection of enlarged bilateral cervical lymph nodes were carried out.

Both thyroid lobes were diffusely enlarged and firm. On the cut surfaces (Fig. 1 b), a poorly defined nodular area 1.5 cm in diameter was found in the right lobe which was more granular than the remainder of the gland. This lesion imperceptibly merged into the surrounding thyroid which also showed fine streaking in the opposite lobe.

Histologically, the entire thyroid exhibited diffuse interstitial sclerosis and heavy lymphocytic infiltration, frequently forming germinal centers. The nodular lesion consisted of papillary excrescences and predominating solid islands of squamoid cells embedded in a dense fibrous stroma. Numerous psammoma bodies were seen within and in between the epithelial formations. Scattered throughout the remaining tissue, tumour foci of the same kind were found lying within lymphatic capillaries (Fig. 1 c). Cervical lymph nodes from both sides contained metastatic deposits of identical shape. Upon S-100 protein immunocytochemistry, dense (>20 cells per unit field, cf. Schröder et al. 1988) infiltrates of dendritic cells within the tumour islands were stained both in the thyroid and in regional lymph node metastases (Fig. 1 d).

Postoperatively, 131I was administered to ablate residual thyroid parenchyma. The anti-thyroglobulin antibodies were negative after surgery. Thyroglobulin levels went down below detection level after the second course of radioiodine therapy. This result was repeated at 6, 18 and 24 months after surgery together with completely negative total body scans at 6 and 18 months. The patient is given full replacement doses of thyroxine by mouth. She is symptom-free now, 24 months after surgery.

Between 1973 and 1988, 185 papillary thyroid carcinomas were seen at the Institute of Pathology, AKH. Reclassification in one of these cases led to the diagnosis of DSPC (case 2). The patient was a woman 34 years of age who had noted a progressive painless enlargement of her thyroid two months prior to admission. Physical examination and laboratory tests (showing T3 being slightly elevated) were consistent with thyroiditis. Since enlarged lymph nodes were palpable on both sides of the neck, however, the possibility of thyroid cancer with regional metastases could not definitely be ruled out. Hence, thyroid surgery was performed. Upon investigation of frozen sections, diagnosis of intraglandular spread of solid carcinoma was made, and surgery was completed with total thyroidectomy and resection of palpable lymph nodes.

Macroscopical and histological findings were almost identical to those reported above for Case 1 with the exception that no clearly defined primary lesion was evident. Briefly, widespread dense fibrous stroma with heavy lymphocytic infiltration was seen distorting the thyroid tissue. Small islands of papillary carcinoma with marked squamous metaplasia and abundance of psammoma bodies were scattered throughout. Microscopically, extension through the thyroid capsule and continuous infiltration of cervical soft tissue was observed. Sections of lymph nodes revealed replacement of architecture by neoplasm. S-100 protein immunocytochemistry resulted in the same staining pattern as described before.

Postoperatively, 131I ablation of residual thyroid tissue, external radiation and oral replacement therapy were performed. Whole-body scans were performed four times up to 11 years following surgery. On none of these occasions was a recurrent or metastatic tumour detected. Serum levels of thyroglobulin were found not to be detectable on repeated measurements up to 12 years after surgery. The patient is symptom-free now, 13 years later.

Discussion

Our two tumour cases precisely fulfill the histological criteria listed by Chan et al. (1987) in their detailed description of three DSPC examples. As noted by these authors, sclerosis, psammoma bodies, lymphocytic infiltration and squamous metaplasia are not uncommon findings in PC of the thyroid; however, it is their occurrence in combination, together with the diffuse permeative growth pattern that distinguishes this variant. In each of the five afore-mentioned specimens, the diffuse fibrosis and heavy lymphocytic infiltrate gave the impression of coexistent Hashimoto's thyroiditis (fibrous variant). Thyroid autoimmunity was further suggested by anti-thyroglobulin and/or anti-thyroid microsomal antibodies detected in the serum of three of these patients.

Patients afflicted by Hashimoto's thyroiditis have been shown not to be at increased risk of developing thyroid carcinoma (Holm et al. 1985), while the incidence of thyroid autoimmunity is significantly higher in thyroid cancer patients when compared with normal controls (Pacini et al. 1988). Diffuse lymphocytic thyroiditis and positive antibody tests, shown histologically and serologically in 9.5% (32/338: Hirabayashi and Lindsay 1965) and 23% (138/600: Pacini et al. 1988) of thyroid cancer patients might therefore represent an autoimmune epiphenomenon initiated by the neoplastic process, rather than evidence of genuine pre-existing inflammatory disease (Chan et al. 1987). This assumption is further supported by data indicating that, at variance with normal controls, no age-dependent increase in serum anti-thyroid antibodies is found in thyroid cancer and that the presence of metastatic thyroid tissue seems to be necessary to perpetuate the autoantibody synthesis (Pacini et al. 1988).

Diffuse lymphoytic thyroiditis and thyroid autoimmunity were shown to be present especially frequently in the papillary type of thyroid neoplasia (28/287=9.8%: Hirabayashi and Lindsay 1965, and 96/401=23.9%: Pacini et al. 1988). PC appearing with the particular microscopical pat-

tern of DSPC, however, seems to be a comparatively rare condition, accounting for only 2% of cases in the series of Chan et al. (1987) and for less than 0.5% in our material. "A few instances" and "several cases" of PC matching the morphological and clinical criteria of DSPC have been reported by Lindsay (1969) and Vickery et al. (1985), respectively, yet their actual frequency is not stated. Several other comprehensive studies on the various histological patterns of PC include cases exhibiting some features typical also of DSPC, but do not describe the complete picture of this disease (Carcangiu et al. 1985; Tscholl-Ducommun and Hedinger 1982; Woolner 1971). Nevertheless, it is noteworthy that 30 years ago, a total of six cases of simultaneous occurrence of thyroiditis and papillary carcinoma diffusely infiltrating the entire thyroid were reported by Crile and Fisher (1953) and Dailey et al. (1955), thus anticipating its description in the more recent literature. As far as the data are given, only female patients between 5 and 34 years of age were affected. Since each of the afore-mentioned tumours had in common its occurrence in young patients and its wide dissemination throughout the thyroid (sometimes without evidence of localized primary malignant lesion) thus causing thyroid enlargement clinically, serologically and histologically suggestive of chronic thyroiditis, their definition as a specific subtype of PC termed "diffuse sclerosing variant" by Vickery et al. (1985) appears fully justified.

Vickery et al. (1985), making special mention of a locally recurrent bilateral DSPC case with extrathyroidal extension (corresponding to stage pT4), believe that this variant might behave less favourably than PC in general. This suggestion has been adopted almost literally by the new WHO classification of thyroid tumours (Hedinger 1988), thus raising the question whether unfavourable prognosis might be another common denominator of this tumour type. In the study of Chan et al. (1987), however, despite bilateral involvement and, in one case, regional lymph node metastases, all three patients showed no evidence of disease 1, 10 and 14 months, respectively, after surgery. The two patients presented herein, notwithstanding that their carcinomas were bilaterally disseminated, had bilateral cervical lymphadenopathy and that in one case the tumour had penetrated through the thyroid capsule (pT4) were symptom-free 2 and 13 years, respectively, after thyroidectomy. As further reports on the postoperative course of individual DSPC cases are not available at present, in our opinion definite conclusions on a possibly more aggressive course for this tumour variant can not yet be made. When related to follow-up data of multicentric, bilateral and extraglandularly infiltrating PC of conventional type (Carcangiu et al. 1985; Schröder et al. 1987; Tscholl-Ducommun and Hedinger 1982; Woolner 1971), the data available suggest that the diffuse sclerosing variant carries a better prognosis than classical PC.

The presence of circulating thyroid auto-antibodies has been shown to be neither a positive nor negative factor in the history of thyroid cancer (Pacini et al. 1988). With respect to the frequent association of PC and thyroid auto-immunity, on the one hand, and the rarity of DSPC, on the other, the presumed favourable behaviour of this tumour variant could not be explained by this phenomenon. It is striking, however, that dense infiltrates of S-100 protein positive dendritic/Langerhans cells were observed not only in the three DSPC cases described by Chan et al. (1987) but were seen in our material, and, as cited in the introduction, were also described in four additional examples of this tumour variant by Gómez-Morales et al. (1989). Confirming the results of other authors on a variety of human neoplasms of different sites, we recently showed such cells to be a marker of immunological defense mechanisms of the host against the tumour also in the papillary type of thyroid carcinoma (Schröder et al. 1988). Irrespective of other morphological and clinical features, in our material no single instance of death resulting from cancer occurred among 23 PCs with dense Langerhans cell infiltrate (including 6 tumours of stage pT4), while 9 of 53 (17%) of the remaining patients ultimately died of thyroid carcinoma.

It remains unclear whether dense Langerhans cell infiltration can be regarded as another hallmark of DSPC. All DSPC cases reported so far subjected to S-100 protein immunocytochemistry have been shown to be Langerhans cell-rich neoplasms and apparently followed an indolent clinical course. Hence, the immunocytochemical findings on this particular tumour variant tend to underscore our previous results on the prognostic value of S-100 immunostaining in the papillary type of thyroid carcinoma. In addition, they suggest that the course of DSPC is similar to or even better than PC in general, at least if prominent Langerhans cell infiltration is present.

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