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Cytokeratin 5/6 and P63 immunophenotype of thyroid lymphoepithelial complexes

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ABSTRACT

Thyroid lymphoepithelial complexes (LECos) are rare, being reported in lymphoma, Graves-Basedow disease, Hashimoto thyroiditis, pericarcinomatous thyroid or in the context of branchial cleft-like cysts. Here we report immunohistochemical expression of cytokeratin 5/6, P63 and TTF1 in 6 cases of thyroid LECos. Two cases had carbimazole treatment for hyperthyroidia and Graves disease. Anti-thyroglobulin, -thyroperoxidase or -TSH antibodies were detected in 4 cases. NSAID or poviodone iodine allergy were present in 2 cases. The treatment consisted in total thyroidectomy or lobectomy. Microscopy showed nodular goiter and focal lymphocytic thyroiditis. Basaloid LECos were seen in all thyroids while squamoid LECos in 2. Associated lesions were papillary thyroid microcarcinoma (2 cases), solid cell nest, thyroglosal duct remnant, lymphoepithelial cyst and thymus-parathyroid unit (one case each). Cytokeratin 5/6 was expressed in both squamoid and basaloid LECos along with P63. TTF1 expression was faint or absent. In conclusion LECos may occur in the context of autoimmune thyroiditis or of a specific immune susceptibility background. The expression of CK5/6 and of P63 suggests a squamous differentiation including in the basaloid LECos. The etiologic relevance of these immunostainings remains limited although rather suggestive of a metaplastic process than of migration-abnormalities.

1. Introduction

Thyroid lymphoepithelial lesions, initially reported as a hallmark for thyroid lymphoma, have also been observed in Graves-Basedow disease, Hashimoto thyroiditis as well as in the pericarcinomatous thyroid tissue [1]. The term of thyroid lymphoepithelial complex (LECo) used by Carney for somewhat similar-appearing lesions but in the context of branchial cleft-like cysts might be less prone to a misunderstanding with lymphoma-related lesions [2].

Here we report 6 cases of thyroid LECos diagnosed in the context of focal lymphocytic thyroiditis (FLT) associated to Graves-Basedow disease or goiter.

1.1. Case 1

The patient (woman, 57-years old) presented with hyperthyroidia (treated by carbimazole and levothyrox) and bilateral thyroid nodules. Anti-thyroperoxidase (TPO) (481 UI/ml, normal <9) and -thyroglobulin (TG) (6 UI/ml, normal <4) antibodies were increased. Iodine123 scintigraphy showed heterogeneous hyperfixation (59.5% at 2 hours). The medical history included uterine fibroma, dolico-colon, L4L5 arthrosis and a familial history of thyroid carcinoma (daughter with thyroiditis and papillary thyroid carcinoma and, with breast cancer). The patient was obese (body mass index/BMI 30.7) and had treatments with alprazolam, amitryptilin and escitalopram. A total thyroidectomy was performed for which the histological analysis showed nodular goiter, FLT with LECos (on 2/16 slides), papillary thyroid microcarcinoma (1-mm), several epithelioid and multinucleated giant cell granulomas and a perithyroid thymus-parathyroid unit.

1.2. Case 2

The patient (man 60-years old) presented with a left thyroid nodule. Thyroid function was normal while anti-TG and -TPO antibodies were detected at low levels (30.75 UI/ml, normal <115 and, <5UI/ml, normal <34, respectively). Blood tests also showed increased prothrombin time (127, normal 70–120). Iodine scintigraphy showed moderate intensity of the left lobe and right hypodensity (7.4% at 2 hours). The patient had worked in a cosmetics laboratory and had a familial history of diabetes (both parents and brothers). The medical history included type 2 diabetes (diagnosed 6 years previously), arterial hypertension, depression, tympan retraction and bilateral chronic miritis with incus lysis and mastoid sclerosis). He was obese (BMI 32) and had treatments with metformin chlorhydrate, bisoprolol, lercandipine, seroplex,

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lysanxia. A left thyroidectomy was performed for which the microscopic analysis showed nodular goiter, FLT with LECos (on 2/30 slides) and, a papillary thyroid microcarcinoma (6.5 mm). A postsurgical retropharyngeal abces occurred (treated by antibiotherapy). At follow-up (21 months after the thyroid resection), the patient was diagnosed with a left renal clear cell carcinoma and right eye cataract (treated both by surgery) and, a persistent right adrenal incidentaloma (on imaging procedures).

1.3. Case 3

The patient (man, 52-years old) was diagnosed with dysphagia and compressive euthyroid goiter. The medical history showed povidone iodine allergy, discal hernia, urinary lithiasis. The blood tests showed increased sedimentation rate (25 s at 1 hour and 55 at 2 hours, normal: 6 and 12 respectively), leukocytosis (10,400/mm3, normal 4000–10,000) without formula abnormalities, an increased cephalin activated time (TCA) (130, normal 80–120) and increased Rosner index (15.3%). A right thyroidectomy was performed, which, on histology, showed nodular goiter, FLT with LECos (on 1/36 slides) and a solid cell nest. One year afterwards, the patient had cholecystectomy for lithiasis.

1.4. Case 4

The patient (woman, 42 years) was diagnosed with euthyroid goiter. Iodine scintigraphy showed heterogeneous fixation (16.5% at 2 hours). The medical history showed NSAID (nonsteroid anti-inflammatory drug) and acetylsalicilic acid allergy, smoking habits, lumbar discal hernia with sciatalgia, arterial hypotension, dysmenorhea (treated by sulfate morphine and spasfon) and a familial history of thyroid disease (type non-available). A total thyroidectomy was performed for which the microscopical analysis showed nodular goiter and FLT with LECo (on 1/5 slides). Postsurgical infraclinical hypocalcemia occurred.

1.5. Case 5

The patient (woman, 68-years old) presented with euthyroid goiter and dysphonia. Anti-TPO antibodies were increased (205 UI/ml, normal< 5.2). The medical history showed arterial hypertension, gastroesophageal reflux disease, cholecystectomy (cause NA), infancy/adolescence asthma and 2 infracentimetric nonspecific lung nodules (on imaging procedures) as well as arthrosis and a bilateral carpian canal syndrome (treated by surgery for right severe sensitivo-motor deficit). The patient was obese (BMI 31.6), her treatments included ibersartan, metoclopramide, avanys, lyrica, carbomagnesium, dexery, mizolen. The TCA was increased (134) as well as the Rosner index (18%). The patient also showed leukocytosis (12.5x109/l, normal 4-10x10^9, with normal formula) and an increased C reactive protein. A total thyroidectomy was performed, which on histological examination showed nodular goiter, FLT with left LECos (on 2/10 slides) and a left lymphoepithelial cyst (1.5 cm). Postsurgical infraclinical hypocalcemia occurred. At 4 years postoperatively, the patient showed hypothyroidia in the context of thyroid hormone and carbosylane association.

1.6. Case 6

The patient (50-years old man) presented with hyperthyroidia and Graves disease, treated by carbimazole (intermittent availability), thiamazole and propranolol. Anti-TPO (>600 UI/l, normal< 34) and -TSH (TRAK) antibodies (30.8 UI/l, normal< 1) were increased while anti-TG antibodies were negative. Blood tests showed hyperleucocytosis (12.7 Giga/l, normal 4–10; with normal formula), hypoeosinophilia (24/mm3, normal 100–500) and a high TCA (126; Rosner index non-available). The medical history revealed arm fracture. A total thyroidectomy was performed for which the microscopical analysis showed goiter, FLT with LECo (on 1/29 slides) and a perithyroid thyroglosal cystic remnant (3-mm).

1.7. Thyroid lymphoepithelial complexes

In all six cases, thyroid LECos consisted of small collections of uniform basaloid cells infiltrated by small lymphocytes (basaloid LECos). In two cases (cases 1 and 5), LECos showed squamous differentiation with more ample eosinophilic cytoplasm (squamoid LECos, cases 1 and 5). LECos were multifocal and bilateral in one of the 3 total thyroidectomy cases (case 1). Dystrophic thyroid vesicles were seen at contact to the lymphocytic follicles, in continuity or not with LECos and, irrespective to the presence of germinal centers in the FLT foci. There was no lymphocyte atypia nor lymphocytic infiltration of vessels.

Immunohistochemistry for cytokeratin CK5/6 (Dako, clone D5/16,134), TTF1 (Dako, clone 8G7G3/1) and P63 (Ventana, clone 4 A4) was performed on a IHC/ISH Benchmark automate (Ventana). Cytoplasmic and/or membrane CK5/6 was expressed by small, basaloid cells, disposed in various patterns: aggregate, rim-reticular or isolated cell-patterns (Figure). Most CK5/6-positive cells in both the basaloid and squamoid LECos expressed nuclear P63. An inconspiciuos basement membrane was seen focally around the periphery of LECos, at contact between the rows/lines of CK5/6 or P63 positive cells and lymphocytes. There was no complete overlap between the CK5/6 and P63-positive cells. Several P63-positive cells were also found in the non-inflammatory thyroid parenchyma. TTF1 expression was heterogeneous and weak.

Both papillary thyroid microcarcinomas (BRAF positive) and the epithelioid and giant cell granulomas were seen in the proximity but non-contiguous with the LECos (when on the same slide) and at distance (other slides). In case 5, numerous CK5/6+ LECos, both basaloid and squamoid, were seen in the lymphocytic cuff of the LE cyst wall. Central discohesion foci were noted in the mural LECos. Several basaloid LECos were also observed at distance from the cyst, on the same slides at 5–7.5 mm or, on other tissue sections of the same lobe. The cyst lining was composed of both non-descript, basaloid and squamoid CK5/6+ cells. Dense fibrous tissue was seen focally between the cyst lining and the lymphocytic cuff. Thyroid follicles were focally intermingled with the lymphocytic cells or separated by fibrous tissue.

2. Discussion

Here we report cytokeratin CK5/6 expression in thyroiditis-associated lymphoepithelial complexes (LECos). While in squamoid LECos the expression pattern paralleled that seen in squamous epithelium, in basaloid LECos, the expression patterns were varied: compact, rim-reticular or isolated cell type. This finding together with P63 expression were suggestive of squamous lineage, possibly immature as the microscopic morphology of expressing cells was nondescript/non-specific, basaloid and their size small. The lack of the layered CK5/6 and P63 expression patterns reported by Caillou [3] may be helpful in the differential diagnosis from thyroiditis-metaplastic-duct lesions which, may belong to the same metaplasia-spectrum. However we have seen one follicle surrounded by a rim of CK5/6+ cells at proximity to one lymphocytic focus with LECo (case 6), reminiscent of the CK6 positive peridermal cells reported in mouse embryo models [4]. Thyroid follicular epithelial dysplasia lesions, known to express P63 [5] were ruled out as based on the cell morphology and lack of follicle formation. The lack of Hassal's corpuscles ruled out the diagnosis of intrathyroid thymus.

The pathogenesis of CK5/6 expression in the small, non-descript, basaloid cells of thyroid LECos remains difficult to elucidate. CK5 is not expressed in the thyroid but by normal myoepithelial or basal cells in squamous or glandular epithelia, without a stratification pattern [6]. The multilayered reticular/rim- or cell aggregate- patterns seen on the CK5/6 immunohistochemistry in the LECos might be explained by the presence of squamous hyperplasia, known to be positive for CK6 [6]. The presence of P63 expression in the LECos might indirectly reflect the role of P63 in cell proliferation and stratification of squamous epithelia as suggested by the presence of an unistratified skin and tongue and oral mucosas in p63 −/− mouse models [7]. Conversely, it can be