Thyroid carcinoma showing thymus-like differentiation: Case presentation of a young man

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Diagnosis is complicated and requires careful histological analysis (CD5- and P63-positive with presence of Hassall’s corpuscles); unfortunately there is no gold standard treatment so, in this case, we administered a sandwich of chemotherapy and radiotherapy.

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Key words: Carcinoma showing thymus-like differentiation; thymic; CD5; Hassall’s corpuscles; Thyroidectomy; Chemotherapy; Radiotherapy

Core tip: Carcinoma showing thymus-like differentiation (CASTLE) is a very rare tumor and is very important to differentiate it from others head and neck tumors because therapy and prognosis are different. Moreover, diagnosis is often complicated. Case reports on this topic, reporting treatment modalities, are useful, because there is no standard treatment for CASTLE.

INTRODUCTION

It is possible for ectopic thymic tissue to be present in the thyroid gland and a carcinoma showing thymus-like differentiation (CASTLE) may arise from such tissue. CASTLE is a rare type of cancer; first described by Miyachio et al[1] in 1981, it was not until 2004 that the World Health Organisation recognised it as an independent clinico-pathological entity and classified it as a type of
the tumour had a lobulated profile and showed marked

groups of squamoid cells similar to Hassall’s corpuscles.

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of poorly differentiated thyroid carcinoma and involve-

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bilateral cervical lymph nodes (Figure 1). Bilateral func-

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Positron emission tomography (PET) scanning did not

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anti-neoplastic therapy was recommended. One month

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with the exception of a suspicious nodule (about 3 cm of
diameter) which was investigated cytologically with FNA

and found to be positive for neoplastic cells (even if the
diagnostic material was poor). The patient consequently

underwent total thyroidectomy. The histological diagno-
sis was a poorly differentiated carcinoma of the thyroid,
pT3N1b (6/6). Immuno-histochemistry (IHC): TTF1-

positive (focal), thyroglobulin-positive (focal), CD56-

positive (focal), NSE- and P63-positive. No adjuvant

anti-neoplastic therapy was recommended. One month

later, ultrasound examination of the neck revealed patho-

tological changes at multiple right lateral cervical lymph

nodes, confirmed by head and neck magnetic resonance.

Positron emission tomography (PET) scanning did not

show distant disease but detected neoplastic activity in

bilateral cervical lymph nodes (Figure 1). Bilateral func-

tional type lymphadenectomy of cervical lymph nodes

was done, with 5/47 lymph nodes positive for metastases

of poorly differentiated thyroid carcinoma and involve-

ment of the right anterior margin of the sterno-mastoid

muscle. About one month later, the patient came to our

hospital for the first time. Physical examination showed

multiple subcutaneous nodules near the surgical scar.

This abnormal evolution of thyroid carcinoma prompted

us to review the histological examinations. We found that

the thyroid was characterised by intra-thyroid tumour

growth including solid nests of epithelioid elements with

high mitotic activity (14 × 10 HPF). There were also
groups of squamoid cells similar to Hassall’s corpuscles.

The tumour had a lobulated profile and showed marked

vascular invasion.

IHC analysis revealed: (1) P63: diffuse and strong

nuclear positivity; (2) CD5: multifocal cytoplasmic posi-
tivity; (3) TTF1: nuclear positivity in the remaining fol-

cicular cells (both in follicles and in the collapsed regions

within the tumour); (4) Thyroglobulin: positivity in the

remaining follicular cells; and (5) Synaptophysin, calcito-

nin, chromogranin, CD56: negative; our revised diagnosis

was CASTLE.

In view of the results of the histopathological review,
a second local relapse within a few months, and a Com-

puted Tomography (CT) scan negative for distant dis-
ease, we planned a therapeutic program which included

chemo-radiotherapy: 2 cycles of chemotherapy, followed

by radiotherapy, followed by 3 further cycles of che-

motherapy using the same regimen. The chemotherapy

administered was carboplatin AUC 6 and paclitaxel 225

mg/m^2 q21. Radiation was delivered by daily volumet-

ric intensity-modulated arc therapy with cone-beam

CT image-guidance. A parotid-sparing simultaneous

integrated boost technique allowed the delivery of three
different dose levels prescribed according to tumour bur-
den: 66.0Gy in 33 fractions on the thyroid bed (site of

macroscopic residual disease), 59.4Gy in 33 fractions on

the right cervical nodes, levels II-V (site of positive extra-
capsular nodes) and a precautionary dose of 54.45Gy

in 33 fractions on left cervical nodes, levels II-V and bi-
lateral recurrent nodes showing excellent clinical response

t.e., disappearance of subcutaneous nodules. The most

significant side-effects during the radiation treatment

were: cervical skin erythaema G2, desquamation in the

thyroid bed, oropharyngeal mucositis G1 and sore throat;

the chemotherapy was well-tolerated. At the end of the

treatment the CT scan was negative and the first follow-

up 3 mo later was also negative.

DISCUSSION

CASTLE is a very rare neoplasm which arises in the thy-

roid gland or the soft tissue of the neck. It is necessary
to differentiate CASTLE from the others tumours such

as primary or metastatic squamous cell carcinoma of

the head and neck or squamous cell thyroid carcinoma,
because the therapy and the prognosis are different[3].

There are two theories of the histogenesis of this cancer,
the first suggests that CASTLE arises from thymic nests

near the thyroid gland which occur as a result of persis-
tence of cervical thymic tissue during embryogenesis; the

alternative theory proposes that it arises from remnants

of the branchial pouches that differentiate along the thy-

mic line[4]. The expression of the IHC marker CD5 by

CASTLE cells provides support for the latter theory[5].

The diagnosis of this disease is complicated by its cyto-

histological presentation. Microscopically it appears to be

arranged in broad, smooth-bordered islands abutting a
desmoplastic cellular stroma[5]. The tumour cells show

squamoid characteristics, having eosinophilic cytoplasm,

oval nuclei and small distinct nucleoli. Within the lymph-

phoid stroma Hassall’s corpuscles may be seen at the

A 26-year-old Caucasian male with no family history of

neoplastic diseases and no comorbidities was examined

by his general practitioner after developing minimal neck

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requested. The first step diagnostic procedures showed

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periphery of the tumour; this may be an additional characteristic of this neoplasm\(^6\). In this case the pathologist was alerted to the possibility of CASTLE by the presence of Hassall’s corpuscles at the review of the histological findings. The IHC analysis showed a tumour that was strongly positive for pancytokeratin, CD5, P63, focal positive for CEA\(^{4,7}\), somewhat positive for chromogranin-A and synaptophysin\(^8\) and negative for TTF-1, thyroglobulin, chromogranin and calcitonin\(^9\) (Table 1). In this case CD5- and P63-positive IHC and the presence of Hassall’s corpuscles were the two most important elements in the diagnosis (Figure 2, 3 and 4). In the literature this neoplasm is considered an indolent, slow-growing cancer even when regional lymph node metastasis is present\(^7,10\). There is no gold standard treatment for this rare lesion although it appears that the first line treatment of choice is surgery with or without adjuvant radiotherapy\(^{15,11}\); we therefore suggested a treatment adapted to the needs of our young patient. We used the type of chemotherapy that we normally give to patients with cancer of the thymus. In this case we administered a sandwich of chemotherapy and radiotherapy. The radiotherapy protocol was similar to that used for thymus tumours, but we reduced the dose intensity because the irradiated volumes were so big that the risk of toxicity for the patient was very high. Currently the patient is feeling well. If this patient had been given radiotherapy after the first surgery would he have relapsed? Unfortunately the literature does not provide evidence on this issue.

A further problem is determining the best radiological technique for staging and follow-up: there are currently no guidelines. In this case we did a total body CT-scan, PET-FDG and MRI of the neck for the staging, but used only a CT-scan for the first follow-up. Although our patient is younger than other cases reported in the literature, we were not able to find epidemiological, genetic or other explanations for his disease. This makes it more difficult to plan follow-up in order to prevent or achieve early diagnosis of other cancers or non-oncological diseases which may arise as ancillary pathological consequences of this rare tumour in this young patient.

**COMMENTS**

**Case characteristics**

A 26-year-old Caucasian male with a history of carcinoma showing thymus-like differentiation (CASTLE).

**Clinical diagnosis**

Neck edema and dysphagia.

**Differential diagnosis**

Metastatic squamous cell carcinoma of the head and neck or squamous cell thyroid carcinoma.

| ICH          | CD5   | Calcitonin | P63   | Synaptophysin | TTF-1 | Thyroglobulin | Chromogranin | CD117          |
|--------------|-------|------------|-------|---------------|-------|---------------|--------------|----------------|
| Anaplastic carcinoma | neg   | Neg        | Neg   | Neg           | Pos/neg | Neg           | Neg          | Neg/pos        |
| CASTLE       | Pos   | Neg        | Pos   | Pos/neg       | Neg   | Neg           | Neg          | Focal pos      |
| Squamous cell carcinoma | Neg   | Neg       | /     | Neg           | Neg   | Neg           | Neg          | Neg/pos        |
| Case report  | Pos   | Neg        | Pos   | Neg           | Focal pos | Neg          | Neg          | /              |

Table 1  Immunohistochemical markers in anaplastic thyroid gland/squamous cell carcinoma to be differentiated from carcinoma showing thymus-like differentiation

Figure 2 Hassall’s corpuscle (arrow).

Figure 3 Diffuse nuclear p63-positive cells.

Figure 4 CD5 positive cells.
**Laboratory diagnosis**
Within normal limits.

**Imaging diagnosis**
The first step diagnostic was an ultrasonography of the thyroid that showed a suspicious nodule, which was investigated cytologically and found to be positive for neoplastic cells.

**Pathological diagnosis**
The thyroid was characterised by intra-thyroid tumour growth including solid nests of epithelioid elements and also groups of squamoid cells similar to Hassall’s corpuscles.

**Treatment**
The patient was treated with surgery followed by a sandwich of chemotherapy and radiotherapy.

**Related reports**
For this case there is no gold standard treatment so we were treated the patient as a patient with a thymic cancer.

**Experiences and lessons**
The importance of a multidisciplinary approach and the case’s sharing could improve patient management.

**Peer review**
The manuscript is well written and reported diagnosis and treatment of a rare case of CASTLE.

**REFERENCES**

1. Miyauchi A, Kuma K, Matsuzuka F, Matsubayashi S, Kobayashi A, Tamai H, Katayama S. Intrathyroidal epithelial thymoma: an entity distinct from squamous cell carcinoma of the thyroid. *World J Surg* 1985; 9: 128-135 [PMID: 3984364 DOI: 10.1007/BF01656263]

2. Cheuk W, Chan JKC, Dorfman DM. Spindle cell tumour with thymus-like differentiation. World Health Organization classification of tumours. In: Delellis RA, Lloyd RV, Heitz PU, Eng C, editors. Pathology and genetics of tumours of endocrine organs. Lyon, France: IARC Press, 2010: 96-97

3. Chan JK, Rosai J. Tumors of the neck showing thymic or related branchial pouch differentiation: a unifying concept.

**Hum Pathol** 1991; 22: 349-367 [PMID: 2050369 DOI: 10.1016/0046-8177(91)90083-2]

4. Reimann JD, Dorfman DM, Nosé V. Carcinoma showing thymus-like differentiation of the thyroid (CASTLE): a comparative study: evidence of thymic differentiation and solid cell nest origin. *Am J Surg Pathol* 2006; 30: 994-1001 [PMID: 16861971 DOI: 10.1097/00000478-200608000-00010]

5. Chow SM, Chan JK, Tse LL, Tang DL, Ho CM, Law SC. Carcinoma showing thymus-like element (CASTLE) of thyroid: combined modality treatment in 3 patients with locally advanced disease. *Eur J Surg Oncol* 2007; 33: 83-85 [PMID: 17085008 DOI: 10.1016/j.ejso.2006.09.016]

6. Da J, Shi H, Lu J. [Thyroid squamous-cell carcinoma showing thymus-like element (CASTLE): a report of eight cases]. *Zhonghua Zhongliu Zazhi* 1999; 21: 303-304 [PMID: 11776823]

7. Ito Y, Miyauchi A, Nakamura Y, Miya A, Kobayashi K, Kakudo K. Clinicopathologic significance of intrathyroidal epithelial thymoma/carcinoma showing thymus-like differentiation: a collaborative study with Member Institutes of The Japanese Society of Thyroid Surgery. *Am J Clin Pathol* 2007; 127: 230-236 [PMID: 17210519 DOI: 10.1309/VM7E52B6U9Q729DQ]

8. Yamazaki M, Fuji S, Daiko H, Hayashi R, Ochiai A. Carcinoma showing thymus-like differentiation (CASTLE) with neuroendocrine differentiation. *Pathol Int* 2008; 58: 775-779 [PMID: 19067852 DOI: 10.1111/j.1440-1827.2008.02310.x]

9. Lam KY, Lo CY, Liu MC. Primary squamous cell carcinoma of the thyroid gland: an entity with aggressive clinical behaviour and distinctive cytokeratin expression profiles. *Histopathology* 2001; 39: 279-286 [PMID: 11532039 DOI: 10.1046/j.1365-2559.2001.01207.x]

10. Roka S, Kornek G, Schüller J, Ortmann E, Feichtinger J, Armbrester C. Carcinoma showing thymic-like elements—a rare malignancy of the thyroid gland. *Br J Surg* 2004; 91: 142-145 [PMID: 14766659 DOI: 10.1002/bjs.4510]

11. Luo CM, Hsueh C, Chen TM. Extraplyrhyd carcinoma showing thymus-like differentiation (CASTLE) tumor—a new case report and review of literature. *Head Neck* 2005; 27: 927-933 [PMID: 15952197 DOI: 10.1002/hed.20237]

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