Surgical management of primary and recurrent carcinoma showing thymous-like elements (CASTLE).

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INTRODUCTION: *Carcinoma showing thymous-like elements (CASTLE) is a rare tumor with only a few cases described in the scientific literature. The aim of the present review is to analyze the data available on the therapeutic options employed in CASTLE tumors and to outline the best surgical management to adopt.*
MATERIALS AND METHODS: *English-language articles published from 1985 through November 2016, and related to CASTLE cases were retrieved using the Pubmed database and specific key-words.*
RESULTS: *Eighty seven cases included in 23 papers, published in the period under investigation, were analyzed in detail. The mean age of the patients was 50.2 years and the male to female ratio 1:1.2. There were performed 31 (35.6%) lobectomies, 29 (33.3%) total thyroidectomies, 15 (17.2%) subtotal thyroidectomies, 4 (4.6%) excisions, 3 (3.4%) partial thyroidectomies, 1 (1.1%) hemithyroidectomy, and 8 (9.2%) additional procedures including tracheal, pharyngeal, and esophageal resections. Lymph node dissection and radiotherapy were associated in 59 (67.8%) and 44 (50.6%) cases respectively. Among the patients with available data 62 (75.6%) were free of disease, 16 (19.5%) were alive with disease, 3 (3.7%) died for the disease, and 1 (1.2%) died for cerebrovascular complications at the time of follow-up. Globally 20 (24.4%) cases of local or distant recurrence were reported. Surgery and radiotherapy, alone or in combination were the treatments most frequently used for recurrences.*
CONCLUSIONS: *CASTLE is a rare tumor which generally respond well to complete surgical resection and adjuvant radiotherapy. These treatments can be further employed for the recurrences, which occur in 24.4% of the cases, along with specific chemotherapy regimens and palliative procedures.*

KEY WORDS: Cancer, CASTLE, Excision, Lobectomy, Thymous-like elements, Thyroidectomy

Introduction

Carcinoma showing thymous-like elements (CASTLE) is a rare tumor described for the first time as an intrathyroidal epithelial thymoma in 1985 by Miyauchi et al., and renamed CASTLE a few years later by Chan and Rosai [1,2]. Since then, 129 cases have been globally reported, prevalently in the form of case reports [2-37]. Only part of these reports contains detailed information about the therapeutic approaches adopted and the outcomes obtained; as a result, no clear guidelines exist to date about the surgical procedures and the multimodality strategies to employ in clinical practice. For this reason, we performed a revision of the current scientific literature in order to analyze the data available on the treatments employed in thyroid CASTLE tumors, and to outline the best surgical management to adopt.

Materials and Methods

English-language articles published from 1985 to November 2016, and related to CASTLE cases were retrieved using the Pubmed database. The search terms

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used were "CASTLE", "carcinoma showing thymous-like elements", "thymous-like differentiation", "intrathyroidal thymous carcinoma", and "thymouslike carcinoma". Titles and abstracts were evaluated in order to include the most relevant studies. References of the selected articles were cross-checked in order to detect papers missed by the search engine.

Results

Among the 129 cases detected, 87 included in 23 papers published in the period under investigation were analyzed in detail [2-36]. Some cases were reported in more than one paper: the early cases published by Miyauchi et al.[1] where also included in the paper of Chan et al. published in 1991 [2]; the later article included also the cases published by Asa et al. [37] and Kakudo et al. [38] in older articles. Cases without relevant information about the surgical management of the disease were excluded, as were duplicates, cases included in reviews, and cases without follow-up information [4,16,21,25,26,31,34].

The articles included, the respective number of cases, and the demographic, clinical and prognostic data of the enrolled patients are summarized in Table 1. The mean age was 50.2 (range 25-79) years, excluding the cases reported by Ito et al. and Veits et al. in which the ages of the single patients were not reported; only 4 (7.1%) of the remaining 56 cases occurred in patients with less than 30 years, and other 5 (8.9%) in those with more than 70 years. Globally, 40 of the 87 patients were males (male/female ratio: 1:1.2).

Data about the treatments adopted for the primary tumors were available in all the cases enrolled. There were performed 31 (35.6%) lobectomies, 29 (33.3%) total thyroidectomies (TT), 15 (17.2%) subtotal thyroidectomies, 4 (4.6%) excisions, 3 (3.4%) partial thyroidectomies, 1 (1.1%) hemithyroidectomy, and 8 (9.2%) additional procedures including tracheal, pharyngeal, and esophageal resections, as well as debulkings and telecobaltotherapy. Lymph node dissection of some type (central neck, cervical unilateral or bilateral, and mediastinal dissections) has been performed in 59 (67.8%) cases, while radiotherapy was associated to surgery in 44 (50.6%) cases. Finally, chemotherapy was used in combination with other treatments in 2 (2.3%) cases.

Survival and data about the clinical conditions of the patients at the time of follow-up were lacking in 5 cases. Among the patients with available data 62 (75.6%) were free of disease, 16 (19.5%) were alive with disease, 3 (3.7%) died for the disease, and 1 (1.2%) died for cerebrovascular complications (Table I). Globally 20 cases of local or distant recurrence were reported, accounting for the 24.4% of the cases. Among them 13 (65%) loco-regional recurrences and 7 (35%) distant relapses were encountered.

Table II summarizes data regarding the types of recurrences found, the treatments adopted and the results obtained. Radiotherapy alone (3 cases, 15%) or in combination with surgery (3 cases, 15%) were the treatments most commonly employed for the recurrences. Surgery alone (2 cases, 10%) and in combination with chemotherapy (1 case, 5%) was also employed. In 2 (10%) cases no treatment was employed because of the poor general clinical conditions of the patients. The exact treatment was not known in 7 (35%) cases. Data about the outcomes of the therapies employed for the recurrences were available in 9 cases: 3 (33.3%) patients were free of disease, 2 (22.2%) were alive with disease, 3 (33.3%) were dead for the disease, and 1 (10.1%) dead for other disease at the time of follow-up.

Discussion

CASTLE are very rare tumors in comparison to other more common cervical malignancies like papillary or follicular carcinomas of the thyroid gland, with only 129 cases reported in the scientific literature since 1985 when the first cases were described [1-36,39]. The pathogenesis of the disease is not known; it has been hypothesized that it arises on ectopic thymic tissue or remnants of branchial pouches, which retain potential for thymic differentiation. Because of its rarity and the non-specific clinical presentation CASTLE is difficult to diagnose, with not well-defined clinicopathological features, and no universally accepted treatment recommendations.

Our review evidenced that most lesions involve and are limited to the thyroid gland; indeed TT or other less-than-total thyroidectomy procedures were reported as the main approaches employed in approximately 90% of the cases. Wider excisions or additional procedures have been described for lesions with a non-thyroidal origin and those with extra-thyroidal extension; notably such procedures require often a sternotomy in order to access the mediastinum and present particular difficulties[40,41]. Yoneda et al. performed a total thyroidectomy in their patient, but they needed also to carry out a segmental resection of the trachea, the right common carotid artery and internal jugular vein, and to reconstruct the common carotid artery [6]. In the case described by Alifano et al. the lesion infiltrated the upper portion of left thymic lobe, and was in close contact with the lower aspect of the left lobe of the thyroid [7]. An en bloc resection of the thymus, sternothyroid muscle, 8 rings of the trachea and the lower aspect of the left thyroid lobe was performed. A termino-terminal tracheal anastomosis was fashioned after laryngeal and tracheal release with dissection of both mainstem bronchi[7]. Chow et al., describe debulking surgical procedures in combination with other treatments in 3 patients with advanced stage [11], while Yamazaki et al. report a total pharyngo-laryngo-esophagectomy, combined with total thyroidecto-

Table I - *Demographic, clinical and prognostic data of the patients enrolled in the review.*

Author	N°	Age	Sex	Treatment	Outcome
Chan et al., 1991[2]	11	25,51,59, 47,65,52, 29,35,59, 43, 69	4M-7F	3 excisions, 3 lobectomies, 1 partial thyroidectomy, 4 subtotal thyroidectomies. LND in 6, Rad in 5 cases.	5 local recurrences (1 DFD, 1 DOD, 3AD),1 distant metastasis (DFD), 5 FOD (1 – 24 years).
Tai et al., 2003[6]	1	34	M	Lobectomy + Rad	FOD at 20 m.
Yoneda et al., 2005[7]	1	54	M	TT + tracheal and carotid resection	FOD at 24 m.
Alifano et al., 2006[8]	1	63	F	Excision + tracheal and thyroid resection + Rad	FOD at 6 m.
Musella et al., 2006[9]	3	70,62,35	2M-1F	3 TT + LND, Rad in 2.	1 recurrence, 2 FOD (22 and 14 m.)
Piacentini et al., 2006[10]	1	47	F	TT + LND + Rad	FOD at 12 m.
Reiman et al., 2006[11]	2	33,37	2 F	Subtotal thyroidectomy, lobectomy	1 FOD at 12 m., 1 NA
Chow et al., 2007[12]	3	43,49,62	2M-1F	2 Debulking , 1 TT, Rad in 3, Chemo in 2 cases.	FOD at 72, 30 and 20 m.,
Ito et al., 2007[13]	25	52 (mean)	11M-14F	6 TT, 9 subtotal, 8 lobectomies, 2 partial lobectomies, LND in 18, Rad in 10.	5 metastases, 2 local recurrences, 15 FOD, 3 NA.
Chan et al., 2008[15]	1	54	M	Lobectomy	FOD at 36 m.
Yamazaki et al., 2008[16]	1	62	M	TT + LND + pharyngoesophagectomy	FOD at 5 m.
Geraci et al., 2011[18]	1	63	M	TT	FOD at 12 m.
Youens et al., 2011[19]	1	52	F	TT + LND + Rad	FOD at 5 m.
Sun et al., 2011[20]	7	56,47,25, 51,56,53, 45	4M-3F	7 lobectomies +LND, Rad in 6 cases.	5 FOD, 2 AD (mean follow-up 34 m.)
Chang et al., 2012[21]	1	34	F	TT	FOD at 27 m.
Huang et al., 2013[23]	1	41	F	TT + LND + Rad	Alive at 12 m. (status NA)
Liu et al., 2013[24]	8	32,62,62, 45,40,79, 52,73	5M-3F	2 TT, 6 lobectomies. LND in all cases. Rad in 7 cases.	FOD at 2, 4, 4, 12, 12, 15, 27 and 45 m.
Tsutsui et al., 2013[25]	6	75,70, 47, 48,70,58	2M – 4F	3 TT, 2 lobectomies. LND in 5, Rad in 1 case.	4 FOD at 113, 67, 38, and 84 m. 1 AD at 66 m., 1 DFD at 137 m.
Nogami et al., 2014[28]	1	52	F	TT + tracheal resection + Rad	DOD at 14 m.
Veits et al., 2014[29]	6	60 (mean)	3M-3F	4 TT + LND, 1 en bloc resection, 1 subtotal, Rad in 4, telecobaltotherapy in 1 case.	1 recurrence at 2 m. 5 FOD at 36, 19, 15, 17, and 22 m.
Hanamura et al., 2015[31]	1	46	M	TT + LND +Rad + Chemo	AD at 32 m.
Zhang et al., 2015[33]	3	37,38,29	1M-2F	2 Lobectomies, 1 TT. LND in 2 cases.	FOD at 6, 26 and 42 m.
Patil et al., 2016[36]	1	34	F	Hemithyroidectomy + LND	FOD at 12 m.

Legend: M: males, F: females, Rad: radiotherapy, LND: lymph node dissection, TT: total thyroidectomy, Chemo: chemotherapy, DFD: dead from disease, DOD: dead from other disease, AD: alive with disease; FOD: free of disease, NA: not available m.: months.

my, followed by reconstruction with a free jejunal graft [15]. Interestingly, all the patients who received such aggressive surgical treatments had excellent results, except for the case published by Nogami et al [27]. In that case a thyroidectomy was initially performed via a neck incision, but the surgeons needed to perform a partial sternotomy to identify the distal portion of the intact trachea, and to mobilize the inferior tracheal segment. The trachea was transversely opened to find the intact portion, and a suprahyoid release was done to mobilize the superior tracheal segment; unfortunately these mobilizations were insufficient and the authors performed a clamshell thoracotomy, and incised the pericardium 360° around the hilum, dissecting the pulmonary ligament

Table II - *Recurrences, treatments and outcomes in the cohort reviewed.*

Treatment	N°	Comment	Outcomes after re-treatment
Radiotherapy	3	One pulmonary recurrence treated with palliative radiotherapy.	1 DFD after 14 months, 2 NA.
Surgery + radiotherapy	3	Recurrences after 9, 19, and 12 years from initial treatment.	2 AD after 18 and 36 months. 1 FOD at 35 months.
Surgery	2	Recurrences after 10 years and 2 months from initial treatment.	1 FOD at 34 months. 1 NA.
Chemotherapy	1	Pulmonary recurrence after 13 months.	NA
Surgery + chemotherapy	1	Recurrence after 22 months.	FOD at 52 months.
Other therapies	1	Nd:YAG ablation + airway stent.	DFD at 8 months.
No therapy	2	Recurrence after 6 months and 17 years from initial treatment.	1 DFD at 24 months, 1 DOD at 12 months.
Not known	7	5 metastases, 2 local recurrences.	NA

DFD: dead from disease, AD: alive with disease, FOD: free of disease, DOD: dead of other disease, Nd:YAG: neodymium-doped yttrium aluminium garnet.

bilaterally. These procedures allowed an end-to-end bronchial anastomosis which was wrapped with an omental pedicle flap, that was lifted up through a retrosternal route via a laparotomy. The patient survived surgery but he had a pulmonary and osseous relapse of the disease and died 14 months after the initial diagnosis[27]. Considering globally the results obtained in patients who underwent aggressive surgery appears evident that wide surgical procedures may produce excellent outcomes, and complete surgical resection should be always attempted, as well as debulking in cases of unresectable disease.

Another interesting issue is the usefulness of the LND, which may increase the incidence of complications like recurrent laryngeal nerve palsy and hypocalcemia [42]. In 67.8% of the cases a LND was performed, including central neck dissection and wider unilateral or bilateral dissections. The pattern followed by most surgeons seems to be that applied in the treatment other thyroid tumors. In absence of clinical and imaging signs of lymph node involvement LND were generally avoided, or lesser dissections were performed; it probably depended on the policy of the single institution and adherence to local or international guidelines. LND were performed more frequently in cases with evident lymph node involvement, and/or extrathyroidal disease. In an older review Roka et al. found that the lymph node status was important for prognosis, and suggested that selective modified neck dissection should always be performed [43]. They also evidenced that, in all patients with negative lymph nodes surgery alone was sufficient. Ito et al. in their article published in 2007 evidenced that the 5- and 10-year survival rates in patients without nodal metastasis were both 100%, whereas the rates in patients with nodal metastasis were 76% and 57%, respectively [12].

Furthermore, none of their patients without extension to adjacent organs died of the disease, whereas the 5- and 10-year survival rates in patients with extension were 92% and 79%, respectively [12]. Sun at al. [19] and Liu et al. [23] performed LND in all their 7 and 8 patients respectively, with excellent results. These evidences suggest that LND should be always taken into consideration, and should be always performed in patients with suspected or evident lymph node involvement.

Radiotherapy and chemotherapy were employed in 44 (50.6%) and 2 (2.3%) cases, respectively. Radiotherapy was generally employed as an adjuvant treatment in patients with unfavorable clinicopathological factors, especially those with residual disease or positive surgical margins, and those with extra-thyroidal and lymph node extension. Chemotherapy was used as induction therapy in 2 advanced stage cases described by Chow et al [11]. The authors employed etoposide and carboplatin, associated with radiotherapy in one case, with satisfactory results [11]. Chemotherapy was also reported in advanced and metastatic patients who did not undergo surgery, and therefore were not included in this review. The most effective combinations seem to be cisplatin and docetaxel, and carboplatin and paclitaxel [29,43].

Recurrences occurred in approximately one fourth of the cases, and 18 of them were treated. In 7 cases the therapies employed were not known; in the remaining cases surgery alone or combined with other treatments was most frequently performed. This reflects the principle mentioned above suggesting that complete surgical resection should be attempted were possible, also in the cases of recurrence. Radiotherapy alone was used in 3 cases: one patient died, and no information are available about the results in the remaining 2 cases, so we cannot evaluate the efficacy of such treatment.

Chemotherapy was used alone and in combination with surgery; the regimens employed were respectively ADOC (cisplatin, doxorubicin, vincristine, cyclophosphamide) + CBDCA-AUC6 (carboplatin, paclitaxel), and CAP (cyclophosphamide, doxorubicin, cisplatin). The global number of cases of recurrence and of the therapies adopted is small, and no clear conclusions can be drawn.

Further well-documented cases are necessary to better understand the clinical behavior of CASTLE, and the optimal therapeutic options useful to avoid and possibly to treat recurrences.

Riassunto

Il carcinoma cosiddetto CASTLE, dall'acronimo inglese "carcinoma showing thymous-like elements", è un tumore raro con solo pochi casi descritti nella letteratura scientifica. Lo scopo di questa review è quello di analizzare i dati disponibili circa le possibili opzioni terapeutiche impiegate nel trattamento dei tumori CASTLE, alfine di valutare quale possa essere il miglior trattamento chirurgico da adottare. A questo scopo sono stati individuati ed analizzati dettagliatamente 23 articoli scientifici relativi a questo tipo di neoplasia, nei quali sono descritti 87 casi, pubblicati in lingua inglese dal 1985 a novembre 2016, utilizzando la banca dati PubMed. L'età media dei pazienti inclusi era di 50,2 anni e il rapporto maschi-femmine 1:1,2. Riguardo al trattamento chirurgico, sono state eseguite 31 (35,6%) lobectomie, 29 (33,3%) tiroidectomie totali, 15 (17,2%) tiroidectomie subtotali, 4 (4,6%) escissioni, 3 (3.4%) tiroidectomie parziali, 1 (1,1%) emitiroidectomia e 8 (9,2%) procedure aggiuntive, tra cui resezioni tracheali, faringee, ed esofagee. La dissezione linfonodale e la radioterapia sono state associate rispettivamente in 59 (67,8%) e 44 (50,6%) casi. Tra i pazienti con dati di follow-up disponibili il 75,6% era libero da malattia, il 19,5% erano vivi ma affetti dalla malattia, il 3,7% erano deceduti a causa della malattia, 1,2% era deceduto per complicanze cerebrovascolari. Globalmente sono stati registrati 20 (24,4%) casi di recidiva locale o a distanza. La chirurgia e la radioterapia, da soli o in combinazione, sono stati i trattamenti più frequentemente utilizzati per le recidive, per le quali sono stati impiegati anche specifici regimi chemioterapici e trattamenti palliativi.

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