

Multimodal treatment of sporadic and inherited neuroendocrine tumors of the thymus

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Background. Neuroendocrine tumors of the thymus (NETT) are a rare tumor entity of the anterior mediastinum. They belong to the category of foregut carcinoids and are often associated with the multiple endocrine neoplasia type 1 (MEN1) syndrome. Approximately 180 cases have been reported since their first description. NETT reveal an aggressive behavior leading to rapid local invasion and metastatic spread. An aggressive surgical approach may achieve long-term survival.

Methods. Patients presenting from 1990 to 2005 at the Department of Surgery and the Department of Gastroenterology of the Philipps-University Marburg with neuroendocrine tumors were enrolled in a prospective database with a follow-up until 2005. Fifty MEN1-patients were enrolled in a study and screening program. These databases were retrospectively reviewed identifying all patients with NETT. The clinical features, therapeutical approaches and the outcome were analyzed.

Results. Six patients were found with NETT, 4 patients suffered from metastases at the time of presentation. All patients were male, with a median age of 41.3 years at presentation. Four out of these 6 patients revealed MEN1 syndrome. All patients underwent tumor resection via sternotomy. Three patients underwent parathyroidectomy and transcervical thymectomy before the NETT was diagnosed. Median survival was 53 months (range, 24–109).

Conclusion. Given a frequent association between MEN1 and NETT, all patients with NETT should be screened for MEN1. Since transcervical thymectomy does not prevent all MEN1 patients from developing NETT, existing surveillance guidelines for MEN1 should consider CT scan of the thorax on a regular basis. (Surgery 2008;144:780-5.)

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NEUROENDOCRINE TUMORS OF THE THYMUS (NETT) are rare neoplasms. In contrast to their nonthymic counterparts, this tumor type is characterized by a highly aggressive behavior, revealing rapid local invasiveness and metastatic potential. In 1972, the first description of NETT was given by Higa and Rosai, differentiating these tumors from thymomas and tumors of an ectopic parathyroid gland.¹ Only about 180 cases have been reported in the world literature to date. Although thymic location of neuroendocrine tumors is a rare finding in patients harboring multiple endocrine neoplasia type 1 (MEN1), an association has been described.² Referring to the published data, NETT

occur in 3–8% of patients with MEN1.³ This is in contrast to the fact that about 30 cases in MEN1 patients have been reported to date, representing nearly 20% of all published cases. All recommendations in the area of NETT are based on retrospective data, mostly from case reports, small series, or reviews. The understanding and management of NETT is of increasing importance in long-term treatment of MEN1 patients. Because of the improved treatment of hyperparathyroidism, pituitary adenomas, and pancreatic neuroendocrine tumors (PET), the development of NETT is becoming a major determinant of long-term survival in MEN1 patients.⁴

In this present study, we report the results of a study on patients with NETTs, resulting from a prospective observation of all patients treated for neuroendocrine tumors and the MEN register at the Department of Surgery in Philipps-University Marburg (Marburg, Germany). These data contribute to the understanding of the clinical symptoms, surveillance, and treatment of NETT in sporadic and MEN1 patients.

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PATIENTS AND METHODS

All patients presenting from 1990 to 2005 at the Department of Surgery and Department of Gastroenterology and Endocrinology of Philipps-University Marburg with neuroendocrine tumors of every origin were enrolled in a database with a follow-up to 2005. Furthermore, 50 patients suffering from MEN1 syndrome were enrolled in a study and screening program and assessed with clinical examination, hormone analysis, and different imaging techniques every other year. These 2 databases were retrospectively reviewed, identifying all patients with sporadic or inherited NETT.

MEN1 patients were identified in agreement with the existing international guidelines for diagnosis and therapy of MEN1 patients, considering only patients with at least 2 of the 3 main MEN1 related endocrine manifestations (parathyroid adenomas, pituitary adenomas, and pancreatic endocrine tumors) and/or one of the main manifestations and proven mutations of the *MEN1*-gene in each case.

All patients except one with suspected MEN1 syndrome underwent DNA mutational analysis after giving informed consent. *MEN1*-gene analysis was provided by Taq cycle sequencing using an automated sequencer (ABI Prism 310; Perkin Elmer, Waltham, Mass) as described previously by our group.⁵ Thymectomy was performed in every patient by median sternotomy due to the size of the tumors. The diagnosis was formulated on the basis of morphology and immunohistochemical reactivity for chromogranin A (CGA), synaptophysin, and neuronal-specific enolase.

RESULTS

Analyzing 448 patients with neuroendocrine tumors and 50 patients of the Marburg MEN1 register at the Department of Surgery, we found 6 patients suffering from NETT. All patients were male (100%), with a median age at presentation of 41.3 years (range, 30–50). Four out of these 6 patients revealed an MEN1 syndrome, whereas 2 patients developed the NETT sporadically, because they did not exhibit further endocrine tumors or a familial cluster of endocrine neoplasias. Concerning the MEN1 patients, the NETT was diagnosed in the context of a periodical screening program. Three of the MEN1 patients developed hyperparathyroidism and underwent parathyroidectomy with bilateral transcervical thymectomy before the NETT was diagnosed. In these cases, the thymic carcinoid was the last clinical manifestation of the MEN1 syndrome. Analysis of the MEN1

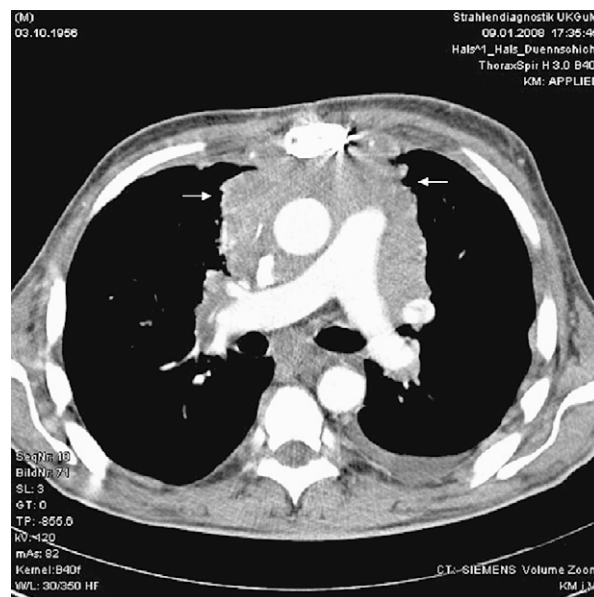


Figure. CT scan of case 3 showing a mediastinal mass with contact to the pericardium (arrows).

gene revealed mutations in 2 cases. One patient revealed 2 typical MEN1-associated endocrine tumors, but a mutation in the *MEN1*-gene could not be detected. In another case, a MEN1 mutation analysis has not been performed due to the death of the patient before the test was available.

In all cases, a computed tomography (CT) scan of the chest was diagnostic (Figure), whereas a MRI was performed. Furthermore, somatostatin receptor scintigraphy (SRS) revealed a significant uptake of the primary tumor and its metastases in all patients except 1 case (Table I). In all patients, urinary hydroxyindolacetic acid tests were negative. Furthermore, circulating CGA levels were elevated in only 1 patient, whereas elevated serotonin levels were detected in another patient. All patients exhibited normal levels for NSE. A sternotomy and thymectomy was performed in all cases. In 4 patients, the NETT invaded the adjacent structures such as pericardium, large vessels and lung.

Metastatic spread of the primary NETT was identified in 4 cases. Lymph node metastases were detected in 1 patient at the left neck, and modified radical neck dissection was performed. In another case, metastases in both adrenals were resected by adrenalectomy and sternotomy was performed 3 times to resect mediastinal lymph node metastasis. In the 3rd case, multiple bone metastases were seen, and a nodule in the skin was identified as metastatic spread. Furthermore, lymph node metastases were detected at the histopathological examination of the resected thymus. In another patient, only multiple bone metastasis

Table I. Main features of the Marburg patients with neuroendocrine thymic tumors

	Age (yr, sex)	Symptoms	MEN1 tumors	MEN1 gene mutation	Octreoscan	Metastases	Follow-up (month)	Outcome
Case 1	40, male	Upper vessel congestion	None	Not performed	Pos.	LN	24	AWD
Case 2	34, male	Cushing	Bilat.AT, PA	Not performed	Pos.	AD, LN, MED	109	DOD
Case 3	30, male	Hoarseness	None	Not performed	Neg.	B, S, LN	34	DOD
Case 4	48, male	None	Bilat. AT, PH	None	Pos.	B	36	NED
Case 5	46, male	None	PH, ZES	Exon10- 466 del14bp	Pos.	None	72	NED
Case 6	50, male	None	PH, PET	None	Pos.	None	48	DURC

AT, Adrenal tumor; PA, pituitary adenoma; PH, parathyroid hyperplasia; ZES, Zollinger-Ellison-syndrome; PET, pancreatic endocrine tumor; Pos., positive; Neg., negative; LN, lymph node; AD, adrenal; MED, mediastinal; B, bone; S, skin; AWD, alive with disease; DOD, death of disease; NED, no evidence of disease; DURC, death of unrelated cause.

in the spine were detected. Two cases revealed no evidence of metastasis.

Several combinations of chemotherapeutics and radiotherapy were performed in 3 patients with metastatic spread. Because of the multiple osteoblastic bone metastases, ^{90}Y -DOTATOC-treatment was performed in 1 case, leading to a survival of 36 months so far. Follow-up was available for all patients. Two patients died due to metastatic spread after 34 and 109 months, respectively. One patient died because of metastasis of a non-functional pancreatic neuroendocrine tumor. One patient was alive with lymph node metastasis 24 months after surgery, whereas 2 patients revealed no evidence of disease 36 and 72 months after surgery.

Tables I and II summarize the features of the Marburg patients with NETT, all surgical procedures and palliative therapies performed.

DISCUSSION

NETT remain a rare tumor entity. As presented in this series, only 6 out of 498 (1.2%) enrolled patients with neuroendocrine tumors or MEN1 suffered from NETT. The median age at diagnosis of 41 years (range, 30–50) in this series is similar to all series that have been published thus far. Nevertheless, 4 patients presented with MEN1 syndrome or developed typical endocrine tumors associated with the MEN1 syndrome. As reported by several authors before, our study confirms the strong prevalence of NETT in male patients.^{3,4} The underlying mechanism explaining these findings might be the influence of male sex hormones on thymocyte proliferation, leading towards thymic tumors in BUF/Mna rats via protein kinase C activity introduced by sex hormones.⁶ In contrast, estrogens act as inhibitors of thymoma growth.⁷

Two major issues still remain a matter of debate: finding the most sensitive imaging

technique, as well as the right treatment for patients suffering from metastasis. NETT are often diagnosed as an undefined mass of the anterior mediastinum. Patients who developed NETT sporadically often present with symptoms due to invasive and expansive growth, such as cough, upper airway, vessel congestion, or hoarseness (eg, cases 1 and 3). In contrast, patients suffering from MEN1 syndrome are usually enrolled in periodical screening programs. As suggested in the international guidelines for diagnosis and therapy of MEN Type 1, chest x-ray should be performed every year, whereas a CT scan of the chest has to be performed only every 3 years.⁸ In chest x-ray films, the profile of the great vessels and the shape of the heart do not allow a diagnosis of NETT until the tumor has reached a metastatic stage or infiltrated into adjacent structures. Therefore, a chest x-ray is not useful in screening or even follow-up of NETT, as it harbors a high chance of missing a NETT, its distant metastases, and/or its early or late recurrences, which occur frequently in NETT (eg, case 2).^{9,10}

In all cases of our Marburg series of NETT, a CT scan of the chest was diagnostic.⁴ Therefore, as suggested by Gibril in her prospective study on NETT in MEN1 patients, the existing surveillance guidelines might need a revision towards the inclusion of a CT scan of the thorax.³

The usefulness of magnetic resonance imaging (MRI) still needs to be established. It may play a crucial role in detecting large vessel or pericardial invasion in a preoperative setting, and is also recommended for early detection of NETT in MEN1.³ Furthermore, MRI reveals a high sensitivity in detecting bone metastases. The use of MRI as a screening tool harbors 2 major disadvantages. First, the costs of MRI examinations are by far higher than those of CT scans, especially when used on a regular basis in a periodical screening

Table II. Therapeutical approaches

	<i>Surgical therapy (including metastases)</i>	<i>Chemotherapy</i>	<i>Radiation</i>	<i>Other therapies</i>
Case 1	ST, PD, ND	SMS-LAR	None	None
Case 2	ST (3x), ADT, LNR	SMS-LAR, INF,	50,4 Gy	None
Case 3	ST, ND	EPI, STC, INF	44Gy+ 33GY	None
Case 4	ST, PD	None	None	90Y-DOTATOC
Case 5	ST, PD	None	None	None
Case 6	ST, ULR	None	None	None

ST, Sternotomy; PD, pericardiectomy; ND, neck dissection; ADT, adrenalectomy; LNR, lymph node resection; ULR, upper lobe lobectomy; SMS-LAR, somatostatin-long acting reagent (lantreotide); INF, interon; EPI, epirubicin; STC, streptococin.

program. Second, as all of our patients underwent sternotomy, the use of MRI as a follow-up tool is not feasible. Therefore, we cannot recommend periodical MRI screening in MEN1 patients.

A further imaging technique performed in our study was SRS. Like other neuroendocrine tumors, NETT express mainly the somatostatin receptor subtype 2, which opens up the possibility of using SRS as a pre- and postoperative diagnostic tool in patients with NETT.^{11,12} In our study, SRS was positive in 5 out of 6 patients, revealing the usefulness of this technique. Furthermore, this test is a powerful tool in detecting distant intra- and extrathoracic metastases that are present in 20–30% of all cases at the time of diagnosis. As another advantage, SRS was able to detect even smaller NETT, and is also helpful in finding other neuroendocrine tumors being associated in MEN1 like pancreatic neuroendocrine tumors (PET). Nevertheless, detecting NETT or metastases by SRS is a prerequisite for the treatment with subcutaneously applied or radiolabeled somatostatin analogues.

Interestingly, in contrast to our findings, Gibril et al evidenced no uptake in bone metastases in their published series.³ The role of somatostatin receptor scintigraphy in detecting small thymic lesions, bone metastases, and early recurrences has still to be elucidated; however, the side effects of finding other neuroendocrine tumors in MEN1 patients and considering the patients for somatostatin analogues treatment make SRS a powerful diagnostic tool.

Regarding the presented MEN1 patients, NETT have not been the first clinical manifestation of the syndrome. Three patients presented with a primary hyperparathyroidism as the first endocrine disorder, whereas 1 patient exhibited bilateral adrenal tumors and a pituitary tumor before. Interestingly, a higher incidence of primary hyperparathyroidism has also been reported in patients with sporadic, nonneuroendocrine thymic tumors, whereas an association of NETT in MEN1 with myasthenia gravis or carcinoid syndrome has not

been reported to date.¹³ In contrast, in one-third of all sporadic cases, Cushing's syndrome has been identified at time of presentation only once in MEN1 patients.¹⁴ Interestingly, 10% of all patients presenting with an ectopic ACTH syndrome harbor a sporadic neuroendocrine carcinoma of the thymus.^{15,16} Furthermore, GHRH secretion and a combination of GHRH and ACTH secretion have been reported in one MEN1 patient and one sporadic patient.¹⁷ Nonendocrine syndromes associated with NETT exhibited polymyositis, pericarditis, or polyarthritis.

Surgery, whenever feasible, remains the treatment of choice in this rare tumor entity. As NETT reveal a rapid local invasiveness and metastatic potential, an aggressive surgical treatment often includes en-bloc resection of the pericardium and atypic resection of the lung. Therefore, median sternotomy should be performed as a surgical approach, and, if necessary, in addition with an anterior or posterolateral thoracotomy to gain a better exposure of the hemithorax. Two groups, led by Fukai and Economopoulos, reported that long-term survival in NETT is only achieved by resection of both the primary tumor and all early or late recurrences.^{18,19} Considering MEN1 patients, the importance of prophylactic thymectomy has been a matter of debate. Unlike Burgess et al, having serious doubts on the efficacy of transcervical thymectomy in the prevention of NETT in MEN1 patients, we recommended this approach in all MEN1 patients in the course of neck exploration for parathyroidectomy to ensure complete resection of intrathymic parathyroid tissue, and to possibly prevent the development of NETT.^{4,20,21} As the present study shows, transcervical thymectomy is obviously not radical enough, but there is also no data available supporting a more radical approach, such as a trans-sternal dissection of the anterior mediastinum, in the prevention of NETT in proven MEN1 patients.

Patients harboring a NETT often present in a late stage of the disease due to the absence of symptoms, leading to a high percentage of patients suffering from metastatic disease at the time of presentation. In these cases, as presented here, surgery seems to be the only therapy improving survival, as effective radio- or chemotherapeutic approaches are still lacking, which underlines the need for prophylactic surgery and a dense surveillance in MEN1 patients. Furthermore, appropriate biochemical markers are also lacking, as only 2 patients presented with elevated levels of either CGA or serotonin. Biochemical markers are not useful for the detection or the surveillance of NETT in MEN1 patients, as concomitant gastroenteropancreatic neuroendocrine tumors of these MEN1 patients have to be taken into account.⁴ One future option might be radiolabelled somatostatin-analogues, as, in our case, ⁹⁰Y-DOTATOC has been useful in one patient suffering from bone metastases. In a recently published study on 177-Lu-octreotate treatment in foregut carcinoids, van Essen et al reported that 1 of the 2 patients suffering from metastatic NETT revealed stable disease after treatment, whereas another patient presented with progressive disease.²² Therefore, the use of radiolabelled somatostatin analogues remains to be further investigated.

In conclusion, an aggressive surgical approach leads to long-term survival in patients with NETT. We recommend transcervical thymectomy in all MEN1 patients in the course of neck exploration for parathyroidectomy to ensure complete removal of all parathyroid glands, but transcervical thymectomy does not prevent all of these MEN1 patients from developing a NETT. Therefore, in accordance to Gibril and Ferolla, we recommend a change of the existing surveillance guidelines in MEN1 patients, considering the inclusion of CT scan of the thorax given the frequent association of NETT with MEN 1 syndrome. Furthermore, all patients with NETT should be screened for the MEN1 syndrome.

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I.V. League



"Doctor, thank you for spending so much time. Now I know that you are informed and that you want me to consent. I don't have a clue about the rest of the explanation."