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Medullary Thyroid Cancer: Case Series Reports and Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Medullary thyroid carcinoma (MTC) is a rare neuro-endocrine tumor that arises from the C-cells of the thyroid. About 20- 25 % of MTC cases may be associated with hereditary syndromes like MEN 2A, MEN 2B and Familial MTC. The survival rate is related mainly to the age of the patient, stage of the disease and completion of the surgical resection.
Methods: Retrospective review of 11 patients who were diagnosed with medullary thyroid cancer in our general surgery department during the period from 2011 to 2021. All patients had preoperative assessment including history taking, clinical examination, tumor marker (calcitonin and CEA), thyroid function testing, ultrasonography and FNAC. All patients underwent genetic assessment to exclude any underlying genetic mutation.
Results: The mean age of diagnosis was 57.73 ± 16.45 years of age. Three patients were males and eight were females. All patients had total thyroidectomy, central and lateral neck dissection except one patient who had prophylactic thyroidectomy due to familial inherited RET mutation. Two patients had recurrence; both of them had high-stage tumor (T3 and T4) with multiple cervical lymph nodes metastasis. The sensitivity of serum calcitonin for the detection of MTC was about

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98%. Patients, who had localized disease and underwent complete surgical resection, had good overall survival rates compared with patients with advanced disease.
Conclusion: MTC represent a heterogeneous group of thyroid cancers. The overall survival is better than that of undifferentiated thyroid cancers. Complete resection of the thyroid tumor and any local or regional metastases provides the only cure for patients with MTC. Further researches are still needed to improve our understanding and management of MTC.

Keywords: Medullary Thyroid Cancer; calcitonin; survival; recurrence, recommendations.

1. INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare tumor that arises from the parafollicular cells (C-cells) of the thyroid gland and accounts for about 2–4% of all malignant thyroid neoplasms [1-2]. Although most cases are sporadic, about 20-25 % of the cases may be associated with hereditary syndromes such as MEN 2A (Sipple syndrome), MEN 2B (Wagenmann-Froboese syndrome) and Familial MTC (FMTC) [1]. The main biomarkers produced by MTC are calcitonin, CEA, Adrenocorticotrophic Hormone (ACTH), chromogranin and others [3]. MEN2A is the most common form of hereditary syndromes associated with MTC. Four variants of MEN2A have been identified; classical MEN2A (MTC, Primary Hyperparathyroidism (PHPT) and pheochromocytom), MEN2A with Cutaneous Lichen Amyloidosis (CLA), and MEN2A with Hirschsprung disease, and FMTC in which the affected individuals have MTC but not pheochromocytomas or Hyperparathyroidism (HPT) [4]. Sporadic MTC usually presents in the fourth to the six decades of life; however, patients with hereditary disease present earlier [5].

The most common presentation of MTC is thyroid enlargement. Lymph node metastases present in at least 35% of MTC patients by the time of diagnosis, while distant metastases occur in approximately 20% of cases. A minority of patients may present with systemic manifestations including diarrhea, flushing, or painful bone metastases [6-7]. The preoperative diagnosis of MTC depends mainly on detecting elevated calcitonin levels and FNAC results. Calcitonin has higher sensibility (nearly 100%) and specificity (95%) [8] while the sensitivity of FNA for the diagnosis of MTC ranges from 12.5% to 88.2% [9]. Contrast-enhanced CT scan, MRI scan, bone scintigraphy and PET-CT scan are recommended in patients with extensive neck disease, suspected regional or distant metastases, and in patients with high serum calcitonin levels greater than 500 pg/mL [1]. Complete surgical resection of the thyroid tumor and any local and regional metastases provides the only cure for patients with MTC [1]. Total thyroidectomy is indicated for all patients with MTC because of the high incidence of multicentricity, the more aggressive course of the disease and the fact that radioactive iodine (131I) therapy is usually not effective for these tumors [10-11]. The American Thyroid Association recommends total thyroidectomy and dissection of the lymph nodes in the central compartment (level VI) for patients with MTC and no evidence of neck lymph node metastases or distant metastases on preoperative imaging [1].

In the current study, we retrospectively reviewed the patients who had medullary thyroid cancer in our general surgery department. We aimed to illustrate our clinical experience with MTC in addition to reviewing the current literature regarding the clinical presentation and management of MTC.

2. MATERIALS AND METHODS

We conducted a retrospective review of patients who were diagnosed with medullary thyroid carcinoma in our general surgery department, during the period from 2011 to 2021. Patients' data were collected from the hospital recording system. Detailed history and clinical examination were obtained for all patients. All patients had biochemical testing including thyroid function tests, serum calcitonin and CEA levels. The suspicion of MTC aroused in patients with thyroid nodule(s) associated with elevated basal calcitonin levels (> 20 pg/ml), with or without a familial history of MTC. Ultrasonography was the initial imaging modality used for the diagnosis of any suspicious thyroid lesion. At the ultrasonography, MTC usually had the appearance of a hypoechogenic solid nodule with frequent microcalcifications, with or without lymph node abnormalities. Diagnosis was made by fine-needle aspiration cytology; uncertain results were reviewed by another pathologist. All patients with extensive disease had staging CT/

PET-CT scan to exclude any distant metastasis. Every individual case was discussed in an endocrine MDT meeting including surgeon, endocrinologist, pathologist and radiologist. All patients had total thyroidectomy and neck dissection according to the tumor spread. Diagnosis was confirmed by final histopathology results. All patients with MTC had RET mutation testing. Family members of RET positive patients were offered genetic testing.

3. RESULTS

11 patients were diagnosed with medullary thyroid carcinoma in our general surgery department. The mean age of diagnosis was 57.73 ± 16.45 years of age. The youngest patient was 23, while the oldest one was 77. Three patients were males and eight were females. Almost all patients presented with neck mass. Two patients presented with metastatic disease. RET mutation was found in two families in our study, one member had prophylactic thyroidectomy and incidental MTC was found in the thyroid gland. Clinical features that raised the suspicion of thyroid malignancy included ill-defined thyroid nodule(s), cervical lymphadenopathy, dysphagia, dyspnea, history of weight loss and/or symptoms of distant metastasis. FNAC from the thyroid and the suspicious lymph nodes was performed in all patients. FNAC sensitivity for the diagnosis of MTC was about 72.7%. Serum calcitonin levels were highly elevated in all patients except the patient who had prophylactic thyroidectomy with sensitivity of about 98%. CEA, although being a non-organ specific tumor-associated antigen, was of help in the diagnosis of MTC; however, it has lower sensitivity rates when compared with calcitonin. Both markers have been used for long term postoperative monitoring to detect any residual or recurrent lesions. CT +/- PET CT scans have been used to evaluate tumor extension and to exclude distant metastasis, (Fig. 1). All patients had total thyroidectomy, central neck dissection and lateral cervical lymph node dissection, except one patient who had prophylactic total thyroidectomy with no lymph node dissection for a positive family history of inherited RET mutation. Eight patients had unilateral neck dissection while two patients had bilateral neck dissection. Cervical lymph node metastasis was found in nine patients mainly in levels Ⅱ, Ⅲ, Ⅳ, Ⅴ and Ⅵ. Five patients had T3 disease, four patients had T1 disease, one was diagnosed with T2 disease and the last one had T4 disease. (Fig. 2). Immunohistochemical staining was utilized to help in the diagnosis and was positive for Chromogranin A, TTF-1, Calcitonin and CEA and negative for thyroglobulin. Six patients had multifocal tumors, while five patients had solitary lesions. Genetic testing was performed in all patients; seven patients had sporadic disease, while four patients had RET mutation. All the four patients who were positive for RET mutation, had either multifocal or bilateral disease. Two patients in our study had mixed papillary (PTC) and medullary (MTC) carcinomas. Two mortalities were reported due to an advanced metastatic disease. Two patients had local recurrence after initial surgery; one after one years and the other one after 2 years post-surgery. (Table 1)

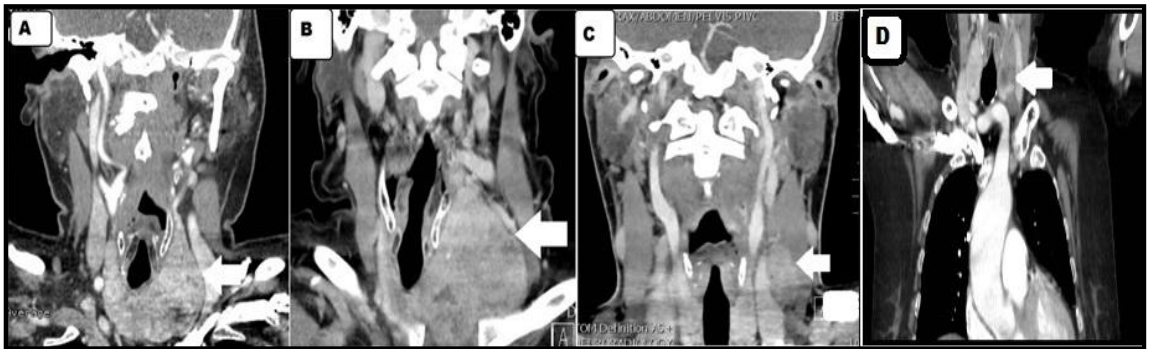

Fig. 1. CT neck: (A) showing heterogeneous thyroid, bulky on the left, deviating the trachea to the right with no evidence of tracheal stenosis or local invasion of surrounding structures, (B) showing a large 6x9 cm left thyroid mass with left retrosternal extension and heterogeneous enhancement characteristics with airway compression, (C) showing enlarged metastatic cervical lymph nodes secondary to medullary thyroid cancer, (D) showing 2.1 x 1.7 cm hypodense heterogeneous mass within the left lobe of the thyroid which indenting the left lateral aspect of the trachea

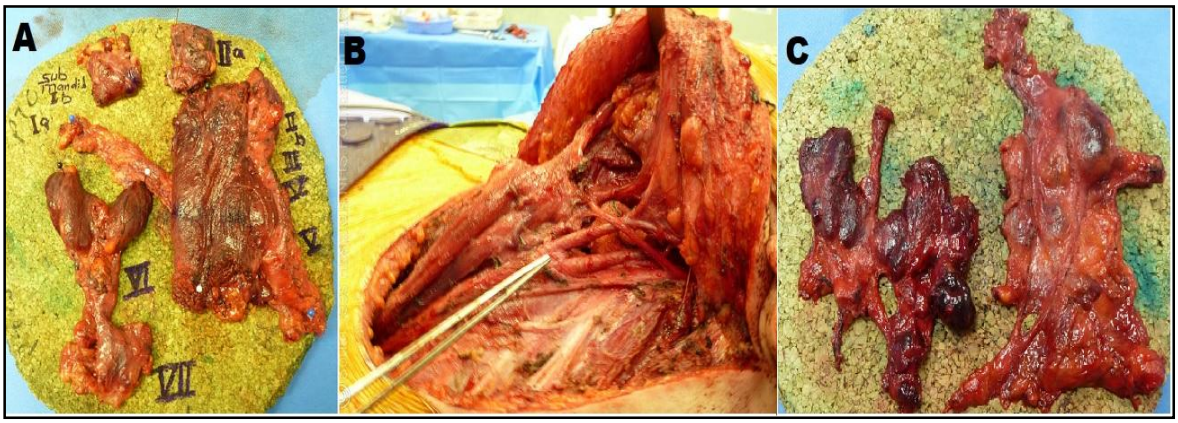

Fig. 2. Neck dissection for medullary thyroid cancer; (A and B) total thyroidectomy with left radical dissection (Note: left sternomastoid muscle, left submandibular salivary gland and left IJV), (C) total thyroidectomy with dissection of level Ⅵ and left levels Ⅱ-Ⅴ

Table 1. Demographic and clinical features of the patients

Variable		Value
Age	Average	57.73 ± 16.45 years 27 years
	Youngest	77 years
	Oldest	
Gender	Male	3 (27%)
	Female	8 (73%)
Clinical presentation	Goiter	8 (73%)
	Distant metastasis	2 (18%)
	Incidental	1 (9%)
LN Dissection	Unilateral	8 (72.7%)
	Bilateral	2 (18)
RET mutation	Yes	4 (36%)
	No	7 (64%)
Histological findings	Unifocal	5 (45%)
	Multifocal	6 (55%)
	MTC	9 (81.8%)
	Mixed MTC and PTC	2 (18.2%)
Stage	T1	4 (36%)
	T2	1 (9%)
	T3	5 (45%)
	T4	1 (9%)
Recurrence	Yes	2 (18%)
MTC related mortality	Yes	2 (18%)

4. DISCUSSION

Medullary thyroid carcinoma (MTC) is a well differentiated thyroid tumor that arises from the parafollicular or calcitonin-producing C cells of the thyroid gland. The C cells originate from the neural crest; consequently, medullary carcinomas have the clinical and histological characteristics of neuroendocrine tumors (unlike other differentiated thyroid carcinomas) such as carcinoids and pancreatic islet cell tumors [12]. C cells produce calcitonin as well as other secretory products such as CEA, Adrenocorticotrophic Hormone (ACTH), chromogranin, histaminases and somatostatin [13]. MTC accounts for about 5–10% of all thyroid malignancies, and 0.4- 1.4% of all thyroid nodules. No significant difference in the distribution between females and males was reported and the main clinical appearance is in the fourth and fifth decades of life [14], although hereditary cases may present earlier. Female to

male ratio in our study was about 2.6:1, and the average age of diagnosis was 57.73 years of age. MTC is responsible for about 13.4% of the total deaths attributable to thyroid cancer [15]. While the 10-year survival rate for patients with a disease limited to the thyroid gland is about 90%, patients with distant metastatic disease have a 10-year survival of only 20% [16]. Two MTC-related mortalities were reported in our study due to an advanced disease with multiple distant metastases by the time of diagnosis.

The pathogenetic mechanism for MTC has been recognized in the activation of the RET proto-oncogene which is located on chromosome 10q11.2 [17]. This oncogene encodes a transmembrane protein receptor which is usually expressed in the cells of the neural crest, branchial arches and the urogenital system. According to the somatic or germline mutation of the activated RET oncogene, two different forms were recognized: the sporadic form, which accounts for about 75%- 80% of cases, and the hereditary or familial form, which accounts for the remaining 20%-25% [18]. The most common hereditary syndromes associated with MTC are MEN 2A (Sipple syndrome), MEN 2B (Wagenmann-Froboese syndrome) and Familial MTC (FMTC). Hereditary MTC is inherited as an autosomal dominant syndrome. MEN2A accounts for about 95% of the MEN2 cases and is characterized by the presence of MTC (95%), PHEO (30–50%) and HPT (10- 20%) [10]. The MEN 2B syndrome accounts for about 5% of the cases of MEN2 and is characterized by MTC, PHEO, ganglioneuromatosis, and Marfanoid habitus. MTC associated with MEN2B develops earlier and has a more aggressive course compared with MTC in other MEN 2 subtypes [19]. Approximately 50% of sporadic MTCs carry RET mutations, and up to 80% of the remaining carry somatic mutations of HRAS, KRAS, or NRAS [20]. All our patients had genetic assessment. Two families in our study were found to have RET mutation; three members of them had MTC, and one had prophylactic total thyroidectomy and incidental medullary micro-carcinomas was discovered in the thyroid gland.

The initial work-up for patients suspected to have MTC should include a complete history and physical examination, measurement of serum calcitonin, CEA, ultrasound of the neck, FNAC, genetic testing for germline RET mutations, and biochemical evaluation for coexisting tumors, especially pheochromocytoma [1]. The most common clinical presentation of MTC includes a palpable thyroid nodule or nodules with or without cervical lymphadenopathy [20]. It was reported that approximately 50% to 70% of patients with MTC have clinically detectable cervical lymph node involvement at the time of diagnosis and about 5% to 10% have distant metastasis [21]. Manifestations of local tumor invasion may include dysphagia, dyspnea, or dysphonia. Patients with extensive metastatic disease may present with diarrhea and flushing (due to increased intestinal motility and impaired intestinal water and electrolyte flux due to high calcitonin levels), weight loss and distant metastasis. Nine patients (81%) in the current study had cervical lymph node metastasis at the time of diagnosis, and two of them (18%) had presented with distant metastasis.

Calcitonin is the most important biomarker for the diagnosis of MTC, as it is useful for diagnosis, surgical planning, follow-up, and prognosis. Calcitonin can present with higher sensitivity (nearly 100%) and specificity (95%) rates [8]. In the current study, the sensitivity of the serum calcitonin for the diagnosis of MTC was about 98%. All our patients had preoperative calcitonin level >1000 ng/L, except the patient who had prophylactic thyroidectomy. Nevertheless, the serum calcitonin levels may increase in other conditions like hypergastrinemia, hypercalcemia, neuroendocrine neoplasms, papillary and follicular thyroid carcinomas and goiter [22]. There is no generalized agreement regarding the routine use of serum calcitonin in the evaluation of thyroid nodules [23]. However, serum calcitonin measurement is recommended in certain circumstances like suspicious cytology and in case of subtotal thyroidectomy [1]. Pre-operative calcitonin levels may correlate with the tumor size in both sporadic and familial cases of MTC [24]. The majority of MTCs also secrete carcinoembryonic antigen (CEA) which can help in both the diagnosis and follow-up of MTC despite being elevated in other non-thyroidal conditions [1].

Ultrasound scan +/- FNAC are the initial investigations used for evaluation of any thyroid swelling. General ultra-sonographic features of a thyroid nodule that increase the likelihood of malignancy includes solid hypoechoic, irregular margins, micro calcifications, rim of calcifications with small extrusive soft tissue component, and/or evidence of extra thyroidal extension [25]. The sensitivity of FNAC for the diagnosis of MTC is about 12.5% to 88.2% [9]. All patients in our study had initial evaluation by ultrasound scan.

Patients with suspicious thyroid nodule(s) and/or cervical lymph nodes had FNAC. FNAC sensitivity for the diagnosis of MTC in our study was about 72.7%. The diagnosis of MTC is confirmed by immunostaining for calcitonin, chromogranin, or CEA [20]. Thyroglobulin staining is usually negative. Occasionally, the diagnosis of MTC can be made only after diagnostic hemi or total thyroidectomy for suspicious or indeterminate FNA results. Computed tomography (CT) is the preferred modality in investigating any neck swelling including thyroid tumors. Classically, MTC on CT appears as hypodense solid masses as the MTC originates from the C-cells and does not usually take up iodine [26]. CT scan, MRI, bone scintigraphy and [18F]-fluorodeoxyglucose positron emission computed tomography (18F-FDG PET/CT) can be utilized to exclude distant metastasis [27]. All new patients with MTC should be screened for RET point mutations, pheochromocytoma, and HPT.

According to the guidelines published by the North American Neuroendocrine Tumor Society, the ATA, and the National Comprehensive Cancer Network (NCCN), complete resection of the thyroid tumor and any local or regional metastases provides the only cure for patients with both sporadic and hereditary MTC [1,11,28]. Because most of these tumors are characterized by multicentricity, aggressive course and poor response to 131I therapy, so total thyroidectomy is the treatment of choice for patients with MTC [1,11]. It was estimated that at least 10% of patients with sporadic MTC and all patients with familial MTC have bilateral or multifocal disease [1]. It was reported that patients with unilateral intra-thyroidal MTC have lymph node metastases in 81% of central compartment (level VI) dissections, 81% of ipsilateral lateral compartment (levels II to V) dissections, and 44% of contralateral lateral compartment (levels II to V) dissections [29].

Preoperative neck ultrasonography and serum calcitonin/CEA levels can help to roughly predict the extent of nodal metastases. It was estimated that patients with basal calcitonin levels greater than 20 pg/mL are more likely to have larger primary tumors and more lymph node metastases [25]. The ATA recommends that patients with MTC and no evidence of neck lymph node metastases by US examination and no evidence of distant metastases should have a total thyroidectomy and dissection of the lymph nodes in the central compartment (level VI) [1]. However, some authors suggest that prophylactic central compartment neck dissection is not required in patients with small intra-thyroidal MTCs with a preoperative calcitonin level less than 20 pg/mL [25].

For patients with lymph node metastases and no distant disease, it was recommended to have total thyroidectomy, bilateral level VI dissection, and dissection of levels II to V in the involved compartment [11]. The ATA recommended that when preoperative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is greater than 200 pg/mL [1]. All patients in our study had total thyroidectomy with central and lateral neck dissection, except the patient with the family history of MTC who had total thyroidectomy only according to the ATA recommendations [1]. Patients with MTC treated with a total thyroidectomy, parathyroid glands should be preserved with adequate blood supply. If the parathyroid viability is not certain, then slivers of the parathyroid should be transplanted into the sternocleidomastoid muscle. In patients with MEN2A and a RET mutation, the parathyroid tissue should be transplanted in a heterotopic muscle, like the brachioradialis muscle in the non-dominant arm due to the higher incidence of PHPT [1].

Levothyroxine (thyroxine, T4) therapy should be commenced immediately after the operation with an initial dose of 1.3 to 1.6 mcg/kg of body weight [30]. Suppression of serum TSH concentrations is not indicated in patients with MTC due to the fact that the C cells are not responsive to TSH.

Postoperative follow-up is necessary for early detection of any recurrent disease. Patients who achieve normal serum CEA and untraceable calcitonin levels are considered biochemically cured with the best prognosis (five-year recurrence rate around 5%) [31]. Postoperatively, the serum calcitonin and CEA concentrations may persist elevated during the first 2-3 months after surgery due to their long half-life in the blood; however, increasing calcitonin and CEA serum levels after this time indicate disease persistence and progression [32]. The ATA recommends that serum levels of calcitonin and CEA, should be measured three months postoperatively, and if within the normal range, they should be measured every six months for

one year, and then yearly [1]. In addition, the ATA recommends that patients with elevated postoperative serum calcitonin levels less than 150 pg/mL should have a physical examination and US of the neck. If the postoperative serum calcitonin level exceeds 150 pg/mL patients should be evaluated by imaging procedures, including neck US, chest CT, contrast-enhanced MRI or three-phase contrast-enhanced CT of the liver, and bone scintigraphy and MRI of the pelvis and axial skeleton to exclude recurrent or metastatic disease [1]. On follow-up of our patients after surgery, only two patients achieved a complete biochemical response (both patients had no lymph node metastasis), while the rest of the patients had calcitonin levels ranging from 36- 200 ng/L with no clinical or radiological evidence of recurrence. On the other hand, progressive elevation of the serum calcitonin level in two of our patients more than 200 ng/L was consistent with a recurrent disease. In the study by Machens et al., it was reported that 62% of the patients with MTC without nodal metastases had normal calcitonin postoperatively, while only 10% of patients with nodal metastasis had normal postoperative calcitonin levels [25]. Both our patients with local recurrence were treated by surgical resection.

Management options for patients with recurrent or residual disease include active surveillance, surgical resection, External Beam Radiation Therapy (EBRT), and directed therapies (such as radiofrequency ablation, cry ablation, embolization), or systemic therapies. Surgical resection of a persistent or recurrent local and regional disease in patients without distant metastases should include compartmental dissection of the positive disease in the central (level VI) or lateral (levels II to V) neck compartments [1]. Adjuvant (EBRT) to the neck and mediastinum is considered for patients with incompletely resected disease and for those who are at high risk for disease recurrence including the presence of microscopic residual disease, extra-thyroidal extension, or extensive lymph node metastases [1]. EBRT has a good effect for local tumor control [32-33].

5. CONCLUSION

Medullary thyroid carcinoma (MTC) is a rare tumor that arises from the thyroid C cells. Its origin, clinical presentation and management are different from differentiated thyroid cancers. Genetic screening for familial syndromes should be performed as a part of the preoperative workup in MTC patients. The tumor response to chemotherapy, radioactive iodine and radiotherapy is poor. Thus, early diagnosis and complete surgical resection provide the only cure for MTC patients. Total thyroidectomy with neck dissection remains the gold standard in the treatment of medullary carcinoma. Further studies are required to improve our knowledge of MTC, to detect other mutations responsible for MTC and to help in the development of new diagnostic and therapeutic strategies.

ETHICAL APPROVAL

Not applicable.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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