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Case report

Circulating epithelial cell enumeration facilitates the identification and follow-up of a patient with early stage papillary thyroid microcarcinoma: A case report

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ABSTRACT

Background: This study examines whether the measurement of circulating epithelial cells (CECs) facilitates the identification and follow-up of a patient with thyroid cancer.
Methods: A 29-y-old woman with no cancer history was enrolled as a healthy control in a CEC study. CECs were enriched from the peripheral blood by the negative selection system PowerMag. Various medical examinations were performed on the patient to establish the diagnosis and to follow-up her disease status during treatment.
Results: This patient had unexpectedly high CEC counts that were sustained for more than two weeks. Thyroid gland ultra-sonography revealed lesions in the left lobe that could not be confirmed as cancer by magnetic resonance imaging, ^{18}F–fludeoxyglucose-positron emission tomography–computed tomography or cytopathological analysis, but were histologically confirmed after thyroidectomy as papillary thyroid microcarcinoma. Both the CEC count and serum thyroglobulin (Tg) concentration were significantly decreased after thyroidectomy, and they and the patient's disease status were correlated during remnant ablation therapy. The CEC count returned to normal when the patient was disease-free 10 months after thyroidectomy.
Conclusions: CEC testing facilitates the identification of individuals at risk for cancer. Longitudinal follow-up of the CEC count may complement serum Tg testing for monitoring the status of patients with thyroid cancer.
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1. Introduction

The annual incidence of thyroid cancer has increased >2.4-fold over the past decade [1–3]. Advancements in diagnostic tools and the rise in disease occurrence both contribute to the elevated incidence of thyroid cancer. More than 90% of thyroid cancers are papillary and follicular thyroid carcinoma. Papillary thyroid microcarcinoma (PTMC) has a tumor size ≤1.0 cm [3] and is usually identified incidentally. While patients with PTMC generally have a favorable prognosis, some of them develop loco-regional lymph node recurrence and distant metastasis that may require an aggressive treatment strategy [4].

Ultrasound-guided fine-needle aspiration is among the first recommended procedures for the cyto-pathological diagnosis of thyroid cancer [5,6]. This procedure is highly operator dependent. Inadequate sampling results in unsatisfactory sensitivity and accuracy. Repeated aspiration is recommended to improve the detection rate in highly suspicious cases

Abbreviations: ^{18}F–FDG-PET, ^{18}F–fludeoxyglucose-positron emission tomography; anti-TgAb, anti-thyroglobulin antibody; CAs, cancer antigens; CECs, circulating epithelial cells; EpCAM, epithelial cell adhesion molecule; MRI, magnetic resonance imaging; PTMC, papillary thyroid microcarcinoma; rhTSH, recombinant human thyrotropin; Tg, thyroglobulin; Tg-IRMA, Tg-immunoradiometric assay; TSHR, thyroid-stimulating hormone receptor.

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[5]. Considerable effort has focused on identifying novel diagnostic biomarkers for thyroid cancer. Circulating microRNA [7], specific gene mutations [8] and circulating epithelial cells (CECs) [9,10] have been explored as prognostic or predictive factors in thyroid cancer.

The first report of the presence of CECs in the bloodstream was proposed in 1869 [11]. The finding of approximately 1 CEC per 10^9 normal blood cells makes it difficult to consistently detect and enumerate CECs, thereby limiting its clinical usefulness. That situation has changed due to recent advances in modern biomedical technologies, such as rare cell isolation, automated cell enumeration, and single-cell gene expression analysis. CECs are now reported as liquid biopsies to assess the treatment response and prognosis for solid cancers, including breast, lung, head and neck and prostate cancers [12–16]. CECs have been detected in the peripheral blood of patients with early stage breast cancer [17]. All studies to date have examined CECs in a defined population with known cancer diagnoses. The question posed is whether CEC testing can be a tool to facilitate cancer detection in individuals without a history of cancer.

2. Case report

A 29-y-old healthy woman was enrolled in a CEC clinical trial as a donor in the control group (CTCHNSCC01, NCT01884129, registered at *www.clinicaltrial.gov*). The Institutional Review Board of Chang Gung Memorial Hospital approved the protocol (approval IDs: 101-2161C and 102-3433B). An informed consent document was signed by the patient before any procedure was carried out in this study.

CECs were enriched by the PowerMag system. This method was shown to efficiently enrich CECs from patients with cancer [16,18]. The system uses a magnetic chamber and a separation bead-packed column for the enrichment of CECs by depleting $CD45^+$ cells. CECs were defined as cells that were positive for epithelial cell adhesion molecule (EpCAM) by immunofluorescence staining (Supplementary Materials and Methods). CECs are not found in the circulation of healthy individuals. The patient reported in this study had a CEC count of 510 cells/ml of blood. Two weeks later, the CEC count was still high (470 cells/ml), excluding the possibility of a false-positive result. Several serum tumor markers, including carcino-embryonic antigen; cancer antigens (CAs) CA15-3, CA-125, and CA19-9; and squamous cell carcinoma (SCC) antigen, were also measured. All of the serum tumor markers were normal with CEA < 0.5 ng/ml (reference: <5.0 ng/ml), CA15-3 equivalent of 9.3 U/ml (reference: <30.0 U/ml), CA-125 equivalent of 27.8 U/ml (reference: <35.0 U/ml), CA19-9 equivalent of 9.1 U/ml (reference: <37.0 U/ml), and SCC antigen equivalent of 1.3 ng/ml (reference: <2.5 ng/ml), respecitvely (Supplementary Table 1).

No obvious signs of malignancy in the chest, abdomen, or breast were identified on physical examination. Slight enlargement of the thyroid gland with nodularity was noted. The patient has never been pregnant with regular menstrual cycle. The patient requested further testing to exclude the potential risk of an occult malignancy in her viscera. Whole body magnetic resonance imaging (MRI) and ^{18}F–fludeoxyglucose-positron emission tomography–computed tomography (^{18}F–FDG-PET–CT) were performed. The only abnormality following the multiple examinations was benign multi-nodular goiters in the thyroid with no sign of extra-thyroid invasion or regional enlarged lymph nodes as revealed by MRI (Supplementary Fig. 1A–F). The left lower thyroid lobe had a standardized uptake value of 2.8 as defined by ^{18}F–FDG-PET–CT (Fig. 1A and B).

Several thyroid-related examinations were then performed to define the clinical significance of the thyroid lesions. The levels of serum thyroid-stimulating hormone (TSH) and free thyroxine (free T4) as measured by using the Siemens Thyroid Assay Reagents (Siemens) were 0.6 μIU/ml (reference range 0.4–5.5 μIU/ml) and 1.0 ng/dl (reference range 0.8–1.6 ng/dl), respectively. Multiple thyroid nodules with abnormal vascularity were identified by thyroid ultrasonography. Microcalcifications were noted in a hypoechogenic nodule of the left thyroid (Fig. 1C). A follicular lesion of undetermined significance was identified by fine-needle aspiration, and an initial serum anti-thyroglobulin antibody (anti-TgAb) test was negative.

Based on laboratory data, imaging studies, and thyroid-related examinations, it appeared that the patient had thyroid lesions with no indication of malignancy. Studies of patients with benign breast disease and hyperthyroidism had <0.1 CEC per 7.5 ml of blood [19]. The unusually high CEC counts (510 and 470 CECs/ml) and undetermined follicular lesion of the thyroid gland in this patient raised concerns that she had a thyroid malignancy. All medical information was fully disclosed to the patient. After discussing the pros and cons of various treatment strategies with the patient, she agreed to a thyroidectomy. During surgery, PTMC was initially diagnosed by histological examination of the frozen section obtained from the thyroid gland. No sign of lymph node involvement was observed. Total thyroidectomy without lymphadenectomy was performed. No complication was found during and after total thyroidectomy. The final pathological report confirmed the diagnosis of PTMC with solid sheets or follicles with focal calcification and stromal invasion (Fig. 2).

The CEC count and level of serum Tg were measured 2 weeks after total thyroidectomy. The patient then received recombinant human thyrotropin (rhTSH) stimulation and underwent remnant ablation with 1.1 GBq (30 mCi) of ^{131}I. The positive immunofluorescent staining signal of the TSH receptor (TSHR) in the CECs and decrease in the CEC count after thyroidectomy (214 cells/ml) were in accord with the idea that the patient's CECs originated from thyroid-related tissues (Fig. 3A and B). Serum Tg was determined using either a Tg-immunoradiometric assay (Tg-IRMA; Cis Bio International) or a chemiluminescent Tg Access assay, a highly sensitive assay with a detection limit <0.1 ng/ml (Beckman Coulter). The post-operative Tg level was 6.3 ng/ml after rhTSH stimulation. A post-treatment whole body scan performed at day 6 after remnant ablation revealed the uptake of radioactive iodine solely in the neck region (Supplementary Fig. 2). The patient was diagnosed with pT1N0M0 stage I cancer.

Both CEC count and Tg testing were performed to monitor the disease status during treatment. Serial follow-up CEC counts showed a strong correlation with the patient's serum Tg and her clinical condition (Fig. 4). Tg was undetectable (<1.2 ng/ml by Tg-IRMA) 1.5 months after surgery, while the CEC count was markedly decreased (31.1 cells/ml), but not within the normal range (<5 cells/ml) [18]. Follow-up 3 months after surgery indicated a trend toward a decrease in the CEC count (24.5 cells/ml) with the accompanying Tg returning to the normal range (<1.2 ng/ml by Tg-IRMA). Eight months after thyroidectomy, the patient achieved a CEC count of 5.5 cells/ml and Tg < 0.1 ng/ml by Tg Access. Ten months after surgery, the patient underwent a 2 mCi ^{131}I thyroid scan. An uptake of 0.4% and a CEC count of 7.3 cells/ml were observed. The patient has achieved a disease-free status and is still closely monitored as an outpatient by an endocrinologist and a medical oncologist.

3. Discussion

The most significant finding uncovered in this study was the unexpectedly high CEC count in an individual who was considered to be in good health. This finding led to the eventual diagnosis of PTMC. Longitudinal follow-up CEC counts revealed that they were closely correlated with the serum Tg levels and the patient's clinical presentation. This case highlights CEC testing as a potential tool to facilitate the identification and management of patients with thyroid cancer.

While the prognostic value of the CEC count has been reported in various cancers [12–16], only a few studies have addressed the clinical impact of CECs on the disease status of thyroid cancer [10]. Dalle Carbonare et al. reported that the expression of Runx2 mRNA in CECs clearly differentiates healthy donors from patients with PTMC [20]. Novosel et al. found that TSHR mRNA-positive patients with PTMC displayed more aggressive histology [21]. Cancer cells were not

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