

World Journal of *Clinical Cases*

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ORIGINAL ARTICLE

Basic Study

- 407 Reliability of Sawai's classification for dental cervical abrasions: A pilot study
Sawai MA, Daing A, Adeel F, Chawla S

Observational Study

- 412 Effect of *Helicobacter pylori* eradication on elder cases: Observational study in community-based medicine
Maruyama M, Kamimura K, Hoshiyama A, Hoshiyama K, Hoshiyama M, Hoshiyama Y, Terai S

CASE REPORT

- 419 Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1
Delvecchio K, Moghul F, Patel B, Seman S
- 423 Human herpesvirus-8 positive iatrogenic Kaposi's sarcoma in the setting of refractory ulcerative colitis
Duh E, Fine S
- 428 Sickle-cell and alpha-thalassemia traits resulting in non-atherosclerotic myocardial infarction: Beyond coincidence?
Nguyen LS, Redheuil A, Mangin O, Salem JE
- 432 Taeniasis: A possible cause of ileal bleeding
Settesoldi A, Tozzi A, Tarantino O
- 437 Do you want to participate in a clinical study as a healthy control? - Risk or benefit?
Giessen H, Nebiker CA, Bruehlmeier M, Spreitzer S, Mueller B, Schuetz P
- 440 Embryonal rhabdomyosarcoma in the maxillary sinus with orbital involvement in a pediatric patient: Case report
de Melo ACR, Lyra TC, Ribeiro ILA, da Paz AR, Bonan PRF, de Castro RD, Valença AMG
- 446 Topiramate induced peripheral neuropathy: A case report and review of literature
Hamed SA

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Editorial Board Member of *World Journal of Clinical Cases*, Andreas G Schreyer, MD, Associate Professor, Department of Radiology, Regensburg University Medical Center, Regensburg 93051, Germany

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 Xiu-Xia Song, Director
World Journal of Clinical Cases
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
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Do you want to participate in a clinical study as a healthy control? - Risk or benefit?

Hanna Giessen, Christian A Nebiker, Matthias Bruehlmeier, Stefan Spreitzer, Beat Mueller, Philipp Schuetz

Hanna Giessen, Beat Mueller, Philipp Schuetz, Department of Internal Medicine, Kantonsspital Aarau, Aarau 5000, Switzerland

Christian A Nebiker, Department of Surgery, Kantonsspital Aarau, Aarau 5000, Switzerland

Matthias Bruehlmeier, Department of Nuclear Medicine, Kantonsspital Aarau, Aarau 5000, Switzerland

Stefan Spreitzer, Department of Pathology, Kantonsspital Aarau, Aarau 5000, Switzerland

ORCID number: Hanna Giessen (0000-0002-2412-7642); Christian A Nebiker (0000-0002-7493-2850); Beat Mueller (0000-0002-1986-2511); Philipp Schuetz (0000-0001-7564-1468).

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Correspondence to: Dr. Philipp Schuetz, MD, Professor, Department of Internal Medicine, Kantonsspital Aarau, Tellstrasse 1, Aarau 5000, Switzerland. philipp.schuetz@ksa.ch
Telephone: +41-62-8386812

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Abstract

A healthy woman volunteered to participate as "healthy control" in a study. An increased level of procalcitonin (PCT) was detected and remained elevated on follow-up measurements. As calcitonin levels were elevated as well, thyroid ultrasound was performed which revealed nodes in both thyroid lobes, one of them showing metabolic activity in positron emission tomography-computed tomography scan. To exclude a malignant thyroid cancer despite the negative findings in a fine needle aspiration the patient underwent thyroidectomy and a medullary thyroid carcinoma (MTC) was detected in the right lobe. MTC is a rare endocrine tumor with a poor prognosis once having spread, therefore early detection remains a priority for the outcome. Screening parameter is serum calcitonin, in absence of infection the pro-hormone PCT can be used as a screening parameter as well with high sensitivity.

Key words: Medullary thyroid cancer; Procalcitonin; Thyroid nodes; Endocrinology; Public health; Healthy control

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Core tip: A lady participating as healthy control in a study was found to suffer from a medullary thyroid cancer, a type of cancer in total surgical removal before the tumor has spread is the most important prognostic factor. The difficulty is the low diagnostic accuracy of ultrasound and procalcitonin-computed tomography scan, as well as the limitations of fine needle aspiration in a patient with several nodules. This case illustrates the consequences

of volunteering as a "healthy control" in a clinical study. While early detection of the MTC was possible in our patient it paid off for her, but abnormal test results may also cause harm to patients if being false positive and leading to invasive procedures.

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INTRODUCTION

In our hospital a study to validate the accuracy of a new assay of procalcitonin (PCT) was conducted and a healthy woman working in our hospital was willing to participate in this study as a healthy control.

PCT is excreted by parenchymatous organs in the presence of bacterial infection. As precursor of calcitonin it is elevated in medullary thyroid cancer (MTC) as well as calcitonin. Frozen serum calcitonin can be used as screening parameter, but several non-specialized laboratories limit the use of calcitonin in MTC^[1].

CASE REPORT

A 57-year-old, previously healthy woman working in the Department of Clinical Pathology of our hospital volunteered to participate as "healthy control" in a study to validate the accuracy of a new PCT assay. She reported to be in good general health condition without signs of ongoing infection or disease. The patient did not smoke or consume large amounts of alcohol and had no signs of malignancy on physical examination or routine blood analysis. Yet, a markedly increased level of circulating PCT of 0.35 $\mu\text{g/L}$ (normal range < 0.03 $\mu\text{g/L}$) was detected, which remained elevated on follow-up measurements for the next 2 mo.

Subsequently, calcitonin levels were found to be elevated as well (33 ng/L, normal range < 5 ng/L). A thyroid ultrasound revealed a goiter with small nodules in both thyroid lobes. There were two suspicious thyroid nodules, a small one lateral in the right thyroid lobe (7 mm \times 5 mm \times 6 mm) and a larger one (10 mm \times 10 mm \times 13 mm) in the left lobe. A fine needle aspiration (FNA) of the bigger node on the left side was done but neither reveal any malignant cells nor was it positive for calcitonin staining, making the existence of a MTC unlikely. To exclude a gastrointestinal neuroendocrine tumor or a small cell lung cancer, both of which have been reported to ectopically produce PCT as well, we decided to perform a ¹⁸F-FDG positron emission tomography-computed tomography (PET-CT), in which the left thyroid nodule detected on ultrasound showed an increased ¹⁸F-FDG uptake. There were no other suspicious lesions in the whole body PET-CT scan (Figure

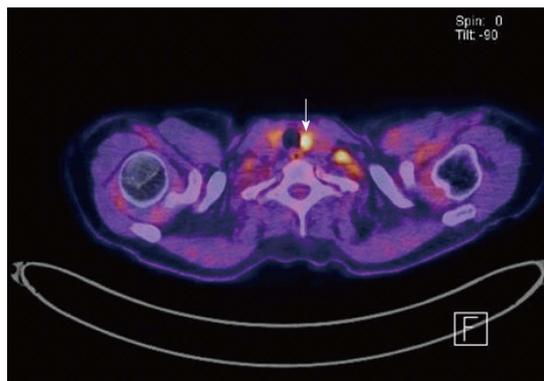


Figure 1 Positron emission tomography-computed tomography scan with ¹⁸F-FDG, 2016 February. Arrow: Left thyroid lobe with metabolic active node.

1).

A previously healthy woman willing to support a scientific study was found to have an elevated level of PCT and calcitonin, a goiter, 2 suspicious nodes in the sonography of the thyroid gland with one of them showing metabolic activity in PET-CT scan.

The case was discussed at our internal tumor board, which recommended total thyroidectomy to exclude MTC despite the negative fine needle aspiration as no other cause of elevations in calcitonin and PCT could be found (Figure 2).

The patient agreed to have surgery which went without complications. The histological evaluation of the thyroid gland showed an (incidental) 3 mm papillary microcarcinoma in the left lobe and a 6 mm medullary carcinoma in the right lobe, inconsistent with the active nodule in the left thyroid lobe in PET-CT. No further neck dissection was done due to the relatively low preoperative calcitonin levels.

Two weeks after surgery the patient came back to the endocrine office. Her PCT and calcitonin levels were now undetectable. We recommended close clinical and biochemical monitoring over the next years. Her prognosis is favorable due to the early recognition of the medullary cancer with small tumor volume, in total resection and no signs of metastasis.

DISCUSSION

This case has three key teaching points relevant for clinical care. First, MTC is a rare endocrine tumor accounting for 8% of all thyroid carcinomas^[2]. With a five year mortality rate of 50%-70% it represents 14% of all thyroid gland related deaths. Early detection and in total surgical removal before the tumor has spread are the most important prognostic factors to lower mortality in this type of cancer. Due to the poor prognosis of medullary cancer once it has spread, early detection remains a priority^[2]. Current guidelines are ambiguous regarding general screening for MTC with calcitonin in the work-up of thyroid nodules, whereas opponents argue it may not be cost-effective^[1,3,4]. The challenge in our patient with incidental MTC is the low diagnostic accuracy of ultrasound and the PET-CT scan. In our



Figure 2 Total thyroidectomy (taken on Jan 17, 2017).

patient, neither test correctly identified or localized the cancer, as retrospectively the metabolically active nodule did not turn out to be malignant. Additionally, fine needle aspiration has limitations particularly sampling bias in a patient with several nodules.

Second, the precursor of calcitonin, PCT became more recently known as an ubiquitously produced biomarker of inflammation and infection. As such it can be used evidence-based in clinical routine guide to diagnosis and antibiotic therapy in respiratory infections and sepsis^[5].

As an endocrine tumor marker in the absence of an infection, an elevated ratio of the procalcitonin to calcitonin indicates worse prognosis in patients suffering from MTC^[6,7].

Last but not least incidental findings of clinical exams, check-ups, laboratory exams and imaging often occur during diagnostic work-up. This case illustrates possible consequences of volunteering as a “healthy control” in a clinical study. While it most certainly paid off for our patient, abnormal test results may also cause harm to patients if being false positive and leading to invasive procedures. In conclusion, it may become important to discuss risks and benefits when “simply” asking a person to volunteer for a clinical study - even if as an allegedly “healthy control”.

ARTICLE HIGHLIGHTS

Case characteristics

Medullary thyroid cancer is a rare cancer that can present with an increased circumference of the throat or a change in voice but is mostly asymptomatic.

Clinical diagnosis

Most medullary carcinoma (MTC) occur sporadic, but in 20% a hereditary

pattern (multiple endocrine neoplasia type 2, men 2) is present, a mutation of the RET protooncogene can be found.

Differential diagnosis

MTC is likely to spread lymphogenic to paratracheal and lateral cervical lymph nodes or hematogenous in liver, lungs and bones.

Treatment

The only curative treatment is the total thyroidectomy with removal of all affected tissue in the neck.

Related reports

Systemic chemotherapy with dacarbazine, 5-fluorouracil or doxorubicin has shown a poor response in only 10%-20%.

Experiences and lessons

Regular measurements of serum calcitonin as tumor marker is used and remission is demonstrated by undetectable serum calcitonin.

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