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Right time to detect urine iodine during papillary thyroid carcinoma diagnosis and treatment: A case report

Zhang SC et al. Urine iodine concentration: True or false?

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Abstract

BACKGROUND
This is the first documentation of a spontaneous and nonspecific chemical reaction of iodinated contrast media with ammonium persulfate used in As\(^{3+}\)-Ce\(^{4+}\) catalytic spectrophotometry for urine iodine concentration (UIC) detection.

CASE SUMMARY
We herein report an incidental case who had a dual source computed tomography examination for papillary thyroid carcinoma diagnosis. Serial spot urine specimens were collected during her hospitalization and were measured by As\(^{3+}\)-Ce\(^{4+}\) catalytic spectrophotometry in a Beckman Coulter AU5800. The reacted solutions were “brownish”, and the results showed extremely high iodine concentrations despite serial dilutions. The patient claimed no dietary habit of iodized salt or iodine-containing medical history, which strongly pointed to iodinated contrast media (ICM) via intravenous injection. Even with 0.01% ICM, its interruption is still profound on the desired urine iodine reaction with ammonium persulfate, leading to inaccurate UIC and possibly inappropriate treatment.
CONCLUSION

The following laboratory suggestions should be considered. (1) As$^{3+}$-Ce$^{4+}$ catalytic spectrophotometry is only suitable for UIC measurement after confirmed ICM renal clearance. (2) A mass spectrometry-based method can be applied as an alternative during the ICM clearance period. (3) The UIC baseline can be confirmed after ICM injection by consecutive detection for at least 2 mo.

**Key Words**: Papillary thyroid carcinoma; Urine iodine concentration; Iodinated contrast media; As$^{3+}$-Ce$^{4+}$ catalytic spectrophotometry

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**Core Tip**: There has been no report on the nonspecific chemical reaction of As$^{3+}$-Ce$^{4+}$ catalytic spectrophotometry thus far. We herein report a typical case and might contribute to improving our understanding of the biochemistry mechanism as well as interpretation of the results of UIC detection during papillary thyroid carcinoma (PTC) diagnosis and treatment. This report also serves as a reminder to establish an individual flowchart to evaluate prognosis during PTC follow-up.

INTRODUCTION

As the most widely used marker to assess the plasmatic iodine pool, urine iodine concentration (UIC) measurement is recommended to assess the iodine status of a population[1,2]. With the increased use of iodinated contrast media (ICM) for chest and neck computed tomography (CT), excess iodine exposure has increased in patients with thyroid disease (TD). Several studies suggest that ICM increases the total body iodine stores for at least 3 mo following contrast exposure and, in some situations, for as long
as two years. The introduction of approximately 0.1% inorganic iodine free from ICM into serum might compete with radioactive iodine or disturb thyroid function due to the Wolff–Chaikoff effect.[34] Considering accurate UIC detection is very important to guide radioactive iodine treatment in patients with TD, it is necessary to understand the effect of excess iodine exposure on UIC after ICM injection in patients with TD.

CASE PRESENTATION

Chief complaints
A 39-year-old female was admitted to our hospital on January 11, 2020 for a re-examination of a thyroid nodule.

History of present illness
The thyroid nodule was found one year ago. Ultrasound examination revealed a 6.1 cm × 4.9 cm × 6.7 cm hypoechoic area in the right lobe of the thyroid gland. The lesion was classified by the thyroid imaging reporting and data system (TI-RADS) as TI-RADS 4C (highly suspected malignancy).

History of past illness
The patient had a medical history that was free of previous illness.

Personal and family history
The patient had no personal or family history.

Physical examination
Upon physical examination, a solid mass was found in the right lobe of the thyroid gland.

Laboratory examinations
Her laboratory blood test results on January 13, including AFP and thyroid function indicators (FT3, FT4, TSH, TPOAb, Tg-Ab, Tg, and PTH), were all within the reference ranges. However, the spot UICs (sUICs) determined on January 14 were reported as errors (Figure 1A-C). We contacted her doctor to obtain new spot urine specimens on January 15 (preoperation) and 17 (1 d before discharge). Each specimen was serially diluted (10-fold, 50-fold, and 100-fold). All sUICs were extremely high (> 3 mg/L, Figure 2). Nevertheless, the reaction curves gradually changed when comparing the same dilution ratio between different specimens over time and finally became valid in 100-fold dilution on January 17. The results indicated that the iodine concentration in the patient was actually dropping.

**Imaging examinations**

On January 13, 2020, the patient underwent dual source CT of the thyroid, and the result indicated a low density, ground-glass enhanced lesion near the back side of the right lobe. No obvious abnormality was found in the left lobe or the isthmic portion. There were multiple nodules in the II, III, IV, and VI regions of the bilateral neck with normal shapes that showed no early-stage enhancement.

**2 FINAL DIAGNOSIS**

The final diagnosis of the presented case was PTC.

**TREATMENT**

The patient underwent radical thyroidectomy on January 15, 2020. Histological examination of the frozen sections from the resected lesion confirmed PTC.

**OUTCOME AND FOLLOW-UP**

The patient had a good recovery. Her thyroid function indicators were normal until this article was written.
DISCUSSION

“Brownish” solution

For the determination of iodine in urine, As$^{3+}$-Ce$^{4+}$ catalytic spectrophotometry is recommended as the standard assay according to WS/T 107.2-2016 by the National Health and Family Planning Commission in China. The protocol is as follows: (1) Add 600 μL ammonium persulfate to 200 μL urine and digest the mixture for 60 min in a 100 °C incubator; (2) Transfer the digested mixture to a Beckman Coulter AU5800; (3) Add 120 μL reagent 1 containing As$^{3+}$ to 25 μL digested mixture; (4) Add 36 μL reagent 2 containing Ce$^{4+}$ to reduce the yellow Ce$^{4+}$ to colorless Ce$^{3+}$; and (5) The decreasing absorbance curve of Ce$^{4+}$ at a wavelength of 410 nm is positively proportional to the concentration of iodine over a designated period of time$^{[5]}$. On January 14, we incidentally found that the digested solution of a spot urine specimen as well as its 2-fold dilution was “brownish”. We contacted the patient, and she recalled that the specimen was collected within one hour after intravenous ICM injection on January 13. The ICM was iohexol (35 g I/100 mL). We tested iohexol instead of urine in serial dilutions. The results strongly indicated that a chemical reaction immediately started once iohexol mixed with ammonium persulfate, even prior to digestion (Figure 3A), and we perfectly reproduced the “brownish” solution as well as the solid purple precipitates (Figure 3B). We believe that this automatic chemical reaction would disrupt the desired reaction of urine iodine with ammonium persulfate and cause inaccurate sUIC values.

ICM clearance

There are three important studies that provide convincing and detailed data on urine iodine clearance$^{[6-8]}$. In general, if a patient undergoes intravenous contrast CT examination, it will take at least 1 mo for the UIC to return to the baseline level. Unfortunately, there is a lack of data for the Chinese population to date. As$^{3+}$-Ce$^{4+}$ catalytic spectrophotometry has a sensitivity of 10 μg/L and a reportable range of 0-3000 μg/L in our laboratory. Notably, the color shade of the spot urine specimen on January 14 was between those of 35 mg iohexol (100% renal clearance assuming 200 mL
urine output) and 3.5 mg iohexol (90% renal clearance). More importantly, as shown in
Figure 1B, the color was faded for the 2-fold dilution and disappeared for the 5-fold
dilution, which allowed us to speculate that the original urine specimen probably
contained at least 17.5 mg iohexol (50% renal clearance). This value was very different
from that calculated on January 14, which was 1.05 mg/L (Figure 1C). We also checked
the Ce⁴⁺ absorbance curve for 3.5 mg iohexol. Consistent with the curve of the 5-fold
dilution of urine specimens on January 14, there was a background optical density
value indicating a nonspecific reaction (Figure 3C and D). Therefore, the spontaneous
and nonspecific chemical reaction of ICM with ammonium persulfate used in As³⁺-Ce⁴⁺
catalytic spectrophotometry can interfere with the accuracy of the UIC results. It is very
important to know the period for urine iodine levels to return to baseline after ICM
injection and to collect urine specimens on the right time.

CONCLUSION
We suggest that the following scenarios should be considered for PTC patients who
may have UIC measurement: (1) Pre-examination quality control of urine specimen.
As³⁺-Ce⁴⁺ catalytic spectrophotometry is only suitable for the determination of the
sUIC as well as the 24-h UIC after confirmed ICM renal clearance; (2) Appropriate
laboratory methods for UIC detection. A mass spectrometry-based method can be
applied as a favorable alternative during the ICM clearance period to evaluate potential
ICM impairment; and (3) Optimal UIC detection intervals. The UIC should be detected
for at least two consecutive months to confirm the baseline after ICM injection.

