Case Report

Regression of papillary thyroid cancer using metformin: a case report

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Abstract: Metformin is a medication that has been used for almost a century for the treatment of type II diabetes. Relatively recent studies have discovered metformin to have utility for the treatment and prevention of number malignancies. Metformin has demonstrated in population studies to reduce papillary thyroid cancer however, the specific effect of metformin on papillary thyroid cancer in humans has not been previously reported. Herein we present the first clinical evidence of anti-tumor effect of metformin on papillary thyroid cancer resulting in clinical regression. This was found in a 35-year-old female who noticed a lump in her neck and was found to have a thyroid nodule. On biopsy, her nodule was proven to be papillary thyroid carcinoma. The patient chose to take metformin in lieu of surgical removal of her thyroid. Repeated monitoring demonstrated clinical regression of her carcinoma, with the size of her nodule decreasing from 1.4×1.1×1.2 to 0.66×0.52×0.67 cm^3, or an 88% reduction in volume. There was also no evidence of any progression to her lymph nodes. This opens a potentially new treatment modality for papillary thyroid cancer which traditionally has had the mainstay treatment options of surgery and radioactive iodine, however more work is needed to be done to confirm the generalizable results for this one case.

Keywords: Papillary thyroid cancer; metformin; nonsurgical cancer management

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Background

Metformin is a biguanide that has been used for almost a century for the treatment of diabetes (1). Over the past two decades, it has been discovered to have utility and the treatment and prevention of number malignancies. Recently, metformin has also come to the attention of endocrinologists as it has been shown to be associated with a preventive effect on thyroid cancer in population-based studies (2) and to exhibit anti-tumor effects in tissue and animal models (3-11). The standard of care for thyroid cancer is thyroidectomy with radioactive ablative iodine (RAI) in selected patients meeting certain parameters based on recent guidelines (12). To our knowledge, the effect of metformin on thyroid cancer in humans has not been reported before. Herein we present here the first clinical evidence of anti-tumor effect of metformin on papillary thyroid cancer. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/aot-18-67).

Case presentation

This is a 35-year-old female who noticed a lump in her neck. Her past medical history includes MTHFR with a pulmonary embolus due to her being on oral contraceptives over 10 years prior to presentation without requiring long term need of anticoagulation, but otherwise no significant past surgical or medical history. She did not have any history of neck radiation or any family history thyroid cancer. She was initially evaluated and managed at outside institution. On ultrasound, she was found at that time to have a 1.4×1.1×1.2 cm^3 nodule involving the right lobe. This nodule was well circumscribed and hypoechoic. The

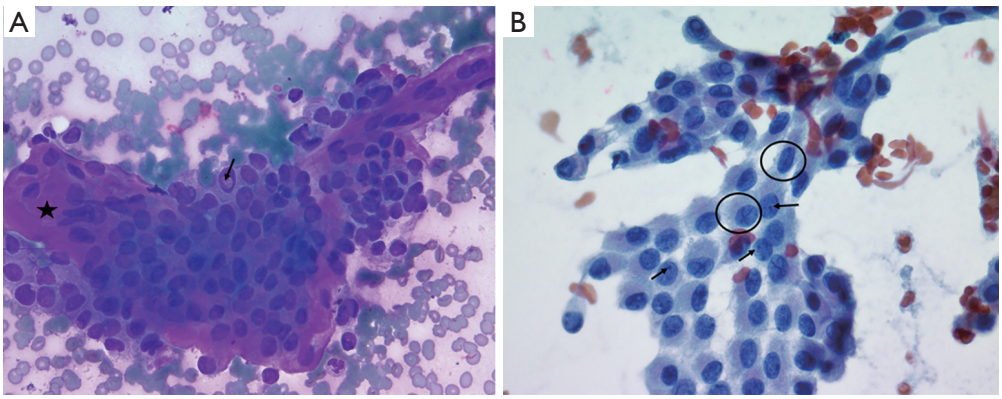

Figure 1 These cytologic slides demonstrate characteristics confirming the diagnosis of papillary thyroid cancer. (A) Papillary thyroid carcinoma showing tumor cells arranged in papillary-like architecture with thick "bubble gum-like" colloid (asterisk) and follicular cell with intranuclear inclusion (arrow), Diff-Quik stain, 40× magnification. (B) Papillary thyroid carcinoma showing sheets of tumor cells with large oval to elongated nuclei, fine chromatin pattern, multiple nuclear grooves (circle) and small eccentrically located micronucleoli (arrow), Papanicolaou stain, 40× magnification.

initial decision was to monitor her without intervention. On a follow-up ultrasound 3 years later, this nodule was found to be 1.5 cm. This nodule was biopsied with FNA at that time showing papillary thyroid carcinoma (*Figure 1*). On neck ultrasound, she did not have any suspicious central or lateral neck lymphadenopathy. The patient declined recommendations for thyroidectomy and based on the literature search, and she was started on 1,000 mg metformin PO BID, along with a ketogenic diet. She then presented to our endocrine surgery center for a second opinion one year later. She was asymptomatic. TSH, FT3 and FT4 were all found to be within normal limits. On exam, her thyroid was nonpalpable and she did not have lymphadenopathy. Neck ultrasound was repeated which showed the right thyroid nodule to be well circumscribed and hypoechoic but decreased in size to 0.66×0.52×0.67 cm^3 (*Figure 2*), with no evidence of central or lateral neck suspicious lymphadenopathy. At this time, she had been on metformin for a year. She was again recommended to undergo surgery, but the patient wished to be monitored with her ongoing metformin and ketogenic diet. Her FNA slides were reviewed at the Cleveland Clinic as well, agreeing with the diagnosis of papillary thyroid cancer. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

Papillary thyroid cancer is one of the most common malignancies seen in the population; currently the 5th most common cancer to afflict women (12). It has also been increasing in incidence, although mortality rates have remained stable at around 1% (12). The traditional treatment plan for this disease involves total thyroidectomy with possible ablation with radioactive I^{131}. Over the past few decades, several studies have demonstrated that this may be overtreatment for lower risk thyroid malignancies. Several low risk thyroid cancers are now being treated with thyroid lobectomy (12). There are some studies monitoring low risk thyroid cancers with routine US surveillance (11).

Metformin was first discovered in 1922 during investigation for treatment of diabetes prior to the widespread availability of insulin. In the 1970s interest was rekindled as a new class of hypoglycemic agents. Over the past two decades, it has been noted that several malignancies have responded or been prevented by metformin, in particular gynecologic, breast, prostate, and colon (13-24). Multiple randomized studies are ongoing to further elucidate the role of metformin in malignancy. This is the first time that papillary thyroid cancer *in vivo* in humans has been demonstrated to respond to metformin.

In the last 10 years, several basic science papers have demonstrated the possible utility of treatment of thyroid cancer. Several have demonstrated decreased growth and increased apoptosis and necrosis from metformin (3,6). They

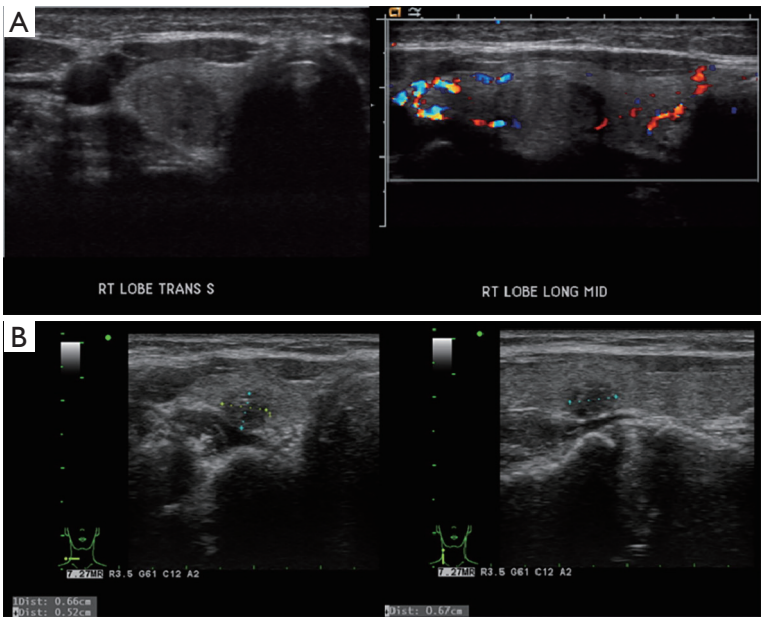

Figure 2 These images demonstrate ultrasound regression of the lesion over a period of 4 years. (A) Initial ultrasound; (B) follow up ultrasound 4 years later.

have also demonstrated potentiation with chemotherapy (10). These apply to all forms of thyroid cancer and not limited to just differentiated papillary and follicular thyroid cancer. Some studies have also demonstrated *in vivo* studies in mice demonstrating regression and increased survival in mice treated with metformin (10).

The mechanism is likely multifactorial. Metformin is used to treat diabetes by allowing peripheral cells to increase insulin sensitivity in healthy cells and decreases gluconeogenesis. There is evidence that this has a diminished effect of insulin sensitivity in cancerous cells thus decreasing their growth. Several other mechanisms including mTor inhibition, AMPK mediate cell retardation, anoikis mediated cell, cell metabolic derangements, anoikis, and potentiation of chemotherapy and radiation have been demonstrated *in vitro* (3,5,6,8-10).

There have been only a few papers in the literature looking at metformin on a clinical setting in the thyroid. Cho *et al.* reported that in the national Korean database, patients who were on metformin were significantly less likely to develop thyroid cancer (2). This finding has been disputed by a similar study looking at the national UK health system (7). One recent paper from Jang *et al.* found a possible increase in disease free survival in diabetic patients on metformin, however this was a limited finding in a subgroup analysis (4). Decrease in nodule size has been observed in limited studies using metformin. Anil *et al.* demonstrated a significant but modest decrease in size of thyroid nodules in insulin resistant patients from 12.9±7.6 *vs.* 11.7±7.2 mm, P<0.0001, however none of these nodules were biopsied in the study (5). A second paper only reached a similar conclusion in nodules <1 cc in size (9). It should be noted that neither of these studies involved any documented cancer.

This study demonstrated biopsy proven cancer with regression. The diagnosis was confirmed by two separate pathologists with review of imaging to confirm regression. Despite this, there are limitations including that this is simply a single case report. Another limitation would include a false positive with the biopsy, however, a thyroid nodule under 1cm would not be an indication for biopsy.

In summary, we report a clinical case related to the effect that metformin may have directly on thyroid cancer clinically. The clinical role needs to be investigated in further studies.

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Footnote

Reporting Checklist: The authors have completed the CARE

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aot-18-67). Dr. EB reports personal fees from Medtronic, personal fees from Ethicon, personal fees from Integra, personal fees from Aesculap, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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