Thyroglobulin "Nonsecretor" Metastatic Poorly Differentiated Thyroid Carcinoma with Noniodine Concentrating Disease and Aggressive Clinical Course: A Clinical Case Series

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Abstract

Poorly differentiated thyroid carcinomas (PDTC) are a subgroup of thyroid cancers with aggressive behavior and worse prognosis compared to the well DTC. Limited diagnostic tools and therapeutic options exist for such cases, and the appropriate management algorithm continues to evolve in this subgroup. They pose difficulty in clinical management due to their behavioral heterogeneity and increased occurrence of aggressive clinical behavior underlining the need for management individualization. In the present communication, a case series of three clinically challenging cases of PDTC (with low serum thyroglobulin (Tg) and iodine nonavidity) are presented with a discourse on their management intrigues, unresolved issues and the requirement of a distinctive management protocol. A small fraction of PDTCs may show low serum Tg values, with the questionable significance of its role for the assessment and monitoring of disease burden in this group of patients. Given uncommon occurrence, limited and variable literature data, management guidelines for "nonsecretor" PDTC needs to be more clearly defined based on scientific evidence. The present clinical case series of PDTC with low serum thyroglobulin in the context of noniodine concentrating metastatic disease and aggressive clinical course ("nonsecretor" status) was noteworthy from this viewpoint.

Keywords: *Fluorodeoxyglucose, positron emission tomography-computed tomography, poorly differentiated thyroid carcinoma, radioiodine scan, thyroglobulin nonsecretor, thyroglobulin*

Introduction

Poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC) constitute a subgroup (~5%–10%) of thyroid carcinoma, of which PDTCs have intermediate prognosis as compared to well differentiated and anaplastic carcinomas of the thyroid.[1,2] The currently accepted model for PDTC oncogenesis is the cumulative accumulation of genetic/epigenetic mutations in a functioning thyrocyte, developing to a well-differentiated cancer cell and then progressing to de-differentiated cancer cell (PDTC or ATC). Along the process of de-differentiation, there is a loss of function, mainly iodine concentrating ability (i.e., sodium-iodide symporter or sodium iodide symporter [NIS] expression) and in a relatively much smaller fraction of cases, the thyroglobulin (Tg) formation, which is evident clinically. BRAF mutations are often associated with this loss of function mechanisms.[3] Serum Tg level is a sensitive tumor marker for thyroid carcinoma: a meta-analysis revealed the negative predictive value of highly sensitive Tg assay was 97% and 99% at basal Tg level of >1 ng/mL and >2 ng/mL as cutoffs for positivity, respectively.[4] Well DTC have relatively defined management algorithms, and they have good prognosis, especially due to the preservation of thyrocyte function. However, PDTCs have a variable clinical profile as evidenced in the literature describing variable radioiodine avidity and Tg secretion. A small fraction of PDTCs may show low serum Tg values (estimate not yet clear in the literature), implying its questionable significance for disease burden monitoring[5-7] in this group of cases. Given all aforementioned reasons, namely, tumor heterogeneity, its less prevalence and variable evidence, management guidelines are not clearly defined in PDTC. We herein present three patients with histopathologically proven

How to cite this article: Kalshetty A, Basu S. Thyroglobulin "nonsecretor" metastatic poorly differentiated thyroid carcinoma with noniodine concentrating disease and aggressive clinical course: A clinical case series. Indian J Nucl Med 2018;33:218-23.

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Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_45_18

Quick Response Code:

but nonfunctioning PDTCs (with both low serum Tg and iodine nonavidity) revealing aggressive clinical course with associated management challenges.

Case Reports

Case 1

A 51-year-old male, reformed chronic tobacco chewer for 10 years and initial Karnofsky performance score of 60 presented with right neck swelling of 2 years duration. He was evaluated earlier outside with ultra sonography (USG) neck and fine-needle aspiration cytology (FNAC) of the thyroid nodule that was suggestive of PDTC. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) undertaken given PDTC at this time, showed 1.7 cm × 1.2 cm sized lesion in the inferior part of left thyroid lobe, a right level Va node and a 1.5 cm × 1.5 cm left level II node. He underwent total thyroidectomy, central compartment clearance with bilateral modified neck dissection, and the histopathology was suggestive of PDTC with metastatic cervical nodes and perinodal extension. Subsequently, he received 150 mCi of ^{131}I therapy given neck residue on the diagnostic I-131 scan and the histopathology. In the posttherapy scan, there was the focus of I-131 uptake observed in the neck. Following a brief of symptom-free period, he presented with neurological symptoms of tingling and numbness in both lower limbs. FDG-PET/CT undertaken showed FDG avid lytic vertebral lesion at D4 and relatively low FDG uptake in the C5–C6 right facetal joint region [Figure 1, left panel]. A follow-up Diagnostic ^{131}I scan following levothyroxine withdrawal methods showed no significant radioiodine uptake [Figure 1, right panel]. Stimulated serum Tg level was 0.647 ng/ml.

A magnetic resonance imaging of the spine showed a soft-tissue mass compressing the dorsal vertebral D4–D5 neural foramina and compressing bilateral D5 nerve roots. Biopsy from the D4 vertebral lesion showed high-grade metastatic carcinoma consistent with that from PDTC. He received palliative external radiotherapy to C4–C6 and D3–D5 vertebrae region (total dose of 30 Gy/10 #) with monthly zolendronate injections for 3 months, with the improvement of symptoms. Subsequently, in 6 months, he presented with generalized weakness and cough. Chest X roentgenogram [Figure 2, upper panel] and contrast enhanced computerized tomography (CECT) thorax showed features suggestive of right pleural metastasis with massive effusion [Figure 2, lower panel]. Pigtail catheter was inserted for symptomatic relief while awaiting FNAC of the pleural metastasis. Histopathology was suggestive of PDTC. The patient died of extensive disease and right pneumothorax after some time.

Case 2

A 32-year-old female, presenting with left thyroid nodule, had undergone total thyroidectomy, the final histopathology suggestive of poorly differentiated carcinoma (PDTC) with the dominantly insular pattern seen in both lobes, and focal cribriform pattern noted. Nuclei of tumor cells showed mild-to-moderate pleomorphism and focal bizarre cells. The tumor was mitotically active of more than 30/10 high power field and areas of necrosis. The tumor infiltrated the parathyroid and soft tissue and reached up to the skin, while the skin was free of tumor. Lymphovascular emboli was noted and the surgical margin was focally involved by tumor with reactive nodes. She subsequently presented with rapidly increasing soft tissue nodule in the suprasternal notch 6 months postsurgery. USG neck revealed a hypoechoic node (1 cm × 0.5 cm) in the right paratracheal region near the thyroid bed and similar echogenic lesion adjacent to it (0.4 cm × 0.7 cm), for which she received external beam radiation therapy (EBRT) to the neck. FDG-PET/CT revealed a low-grade metabolic nodule near the suprasternal notch [Figure 3]. FNAC from the nodule was suggestive of metastatic PDTC. Stimulated Tg at this time was 0.79 ng/ml. CECT neck and thorax undertaken at this time showed residual thyroid lesion in the suprasternal region and a tiny indeterminate lung nodule in right lung upper lobe region, for which she underwent resection of the lesion and reconstruction. The histopathology was suggestive of PDTC. The immunohistochemistry (IHC) was positive for ck7, AE1/AE3, PAX8, and TTF-1. A follow-up CT at 5 months

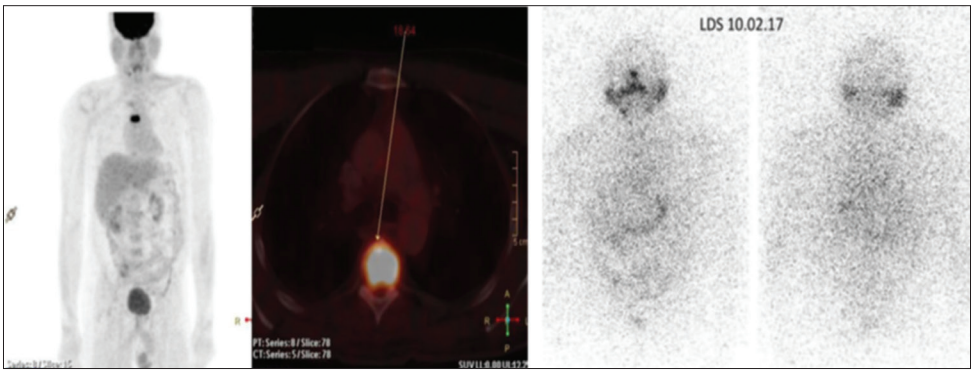

Figure 1: Fluorodeoxyglucose-positron emission tomography/computed tomography [Figure 1, left panel] revealing hypermetabolic lytic lesions in D4 (arrow) and C5–C6 vertebrae. Follow-up low dose ^{131}I diagnostic scan [Figure 1, right panel] did not show abnormal ^{131}I uptake

suggested disease progression [Figure 4, upper panel], however with stimulated Tg of 0.72 ng/ml.

A follow-up FDG-PET/CT at this time was suggestive of rapid disease progression of the FDG avid disease process at the aforementioned sites [Figure 4, lower panel]. A diagnostic I-131 scan (with 2 mCi ^{131}I) showed faint uptake in the neck, and she was treated with 243 mCi RAI (primarily with empirical intent). The posttherapy scan showed the neck and low-grade uptake in lung lesion [Figure 5]. At 4.5 months posttherapy, she recently presented with right neck nodule and left chest wall swelling, gradually increasing over a month and is being counseled and worked up for consideration of starting on tyrosine kinase inhibitors.

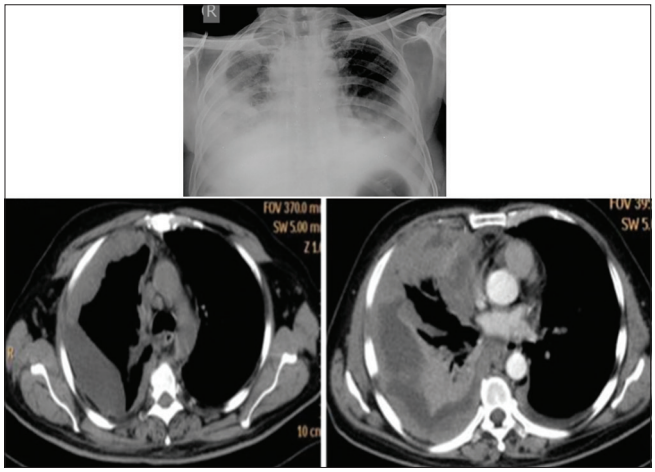

Figure 2: X-ray chest [Figure 2, upper panel] suggestive of right pleural metastases with bilateral pleural effusion (right > left). Contrast-enhanced computerized tomography [Figure 2, lower panel] suggestive of extensive right pleural metastases with collapse of right lung and right pleural effusion. Mild left pleural effusion is also seen

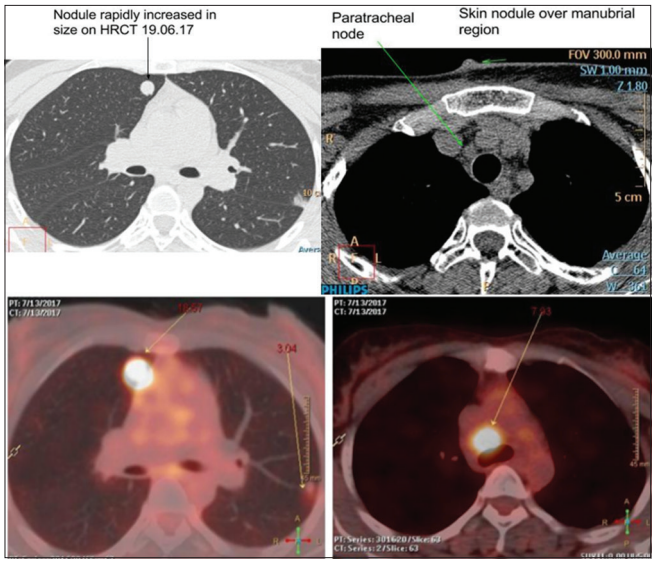

Figure 4: Follow-up HRCT chest [Figure 4, upper panel] showed rapid increase in size of the right lung nodule (black arrow) and a new sub-pleural lesion in upper lobe of left lung. It also showed a right paratracheal node (long green arrow) with cutaneous nodules. Re-staging fluorodeoxyglucose-positron emission tomography/computed tomography [Figure 4, lower panel] demonstrated hypermetabolic bilateral lung nodules (yellow arrows in image on left). It also showed a new metabolically active precarinal node (yellow arrow with SUVmax 7.03). The features were suggestive of rapid disease progression

Case 3

A 49-year-old male initially presented with swelling of right-sided goiter associated with change in voice; FNAC of the thyroid nodule was suggestive of thyroid neoplasm, for which he had undergone total thyroidectomy with right cervical lymph node dissection in an outside Institute. The histopathology was suggestive of papillary carcinoma of the thyroid (pT: 4.1 cm) with lymph nodes showing metastasis with extranodal extension. ^{131}I scan (outside) showed iodine avid foci in the neck and stimulated Tg of 5.11 ng/ml; He was treated with 105 mCi ^{131}I, the posttherapy scan revealing residual neck lesions [Figure 6].

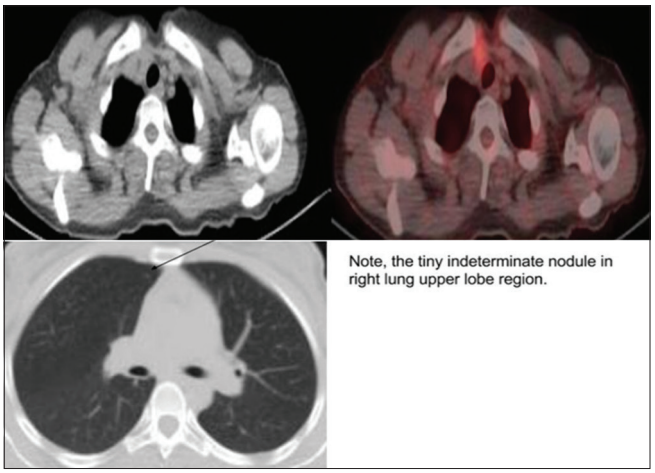

Figure 3: Fluorodeoxyglucose positron emission tomography computed tomography on 03.02.17 showed low grade fluorodeoxyglucose uptake in the ill-defined soft tissue [Figure 3, upper panel] in right para-tracheal region at the supra-sternal notch. Contrast enhanced computerized tomography neck [Figure 3, lower panel] and thorax showing a very tiny indeterminate lung nodule in upper lobe of right lung (black arrow)

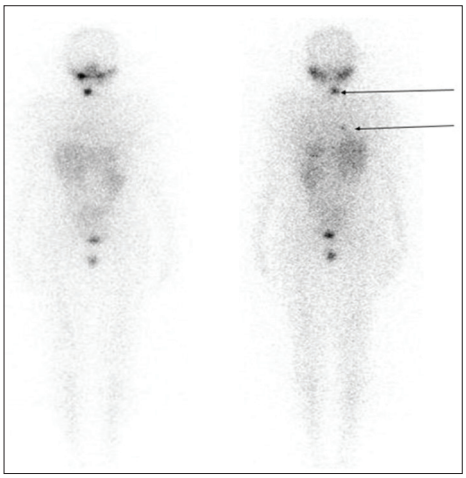

Figure 5: Posttherapy ^{131}I scan demonstrating iodine uptake in neck (black arrow) and in right lung nodule (black arrow)

Subsequently, around 2 months postradioiodine therapy, he presented with complaints of a cough and worsening of hoarseness of voice. CT of the neck revealed mass lesion measuring 4.3 cm × 3.2 cm in right thyroid bed, encasing and infiltrating the trachea, abutting right carotid sheath with enlarged right paratracheal nodes in superior mediastinum ~2.8 cm, enlarged left hilar lymph node measuring 1.6 cm. Enlarged right Level II and right Level III nodes were also noted with overall impression of unresectable disease after review. The HPE review at our Institute revealed poorly differentiated carcinoma arising in papillary thyroid carcinoma. Tumor showed extrathyroidal extension, focal insular pattern, and vascular emboli. Mitotic count was 10–12/10 hpf in the high proliferating area. Tumor also infiltrated adjacent parathyroid gland. He received EBRT to the neck and mediastinum with 6MV intensity-modulated radiation therapy with a dose of 70 Gy/35#. He complained of hoarseness of voice post-EBRT. A CECT thorax after 3 months of EBRT was suggestive of soft tissue in the right thyroid bed, compressing trachea [Figure 7, upper panel]. He was then started on tablet Sorafenib 200 mg twice daily given clinical disease progression. He developed Grade II Hand-foot syndrome and hence discontinued by himself. The FDG-PET/CT at this time showed metabolically active ill-defined soft tissue in right thyroid bed, right cervical nodes, mediastinal nodes with new bilateral lung nodules [Figure 7]. Given previously I-131 avid disease, a diagnostic radioiodine scan was performed which was negative (stimulated Tg ~0.3 ng/ml). A 68Ga-DOTATATE-PET/CT performed to look for the feasibility of peptide receptor radionuclide therapy (after obtaining informed consent), showed Krenning score 2 uptake in the left hilar node only [Figure 7]. He is now being planned and being counseled for multiple options such as restarting of tyrosine kinase inhibitors at tolerable levels versus empirical I-131 therapy. CT-guided biopsy from left para-hilar mass was suggestive of metastatic deposits of carcinoma, consistent with metastasis from the known primary in the thyroid. On IHC, tumor cells showed expression of TTF1, Tg, CK7, focal and weak Napsin-A and are negative for CK20.

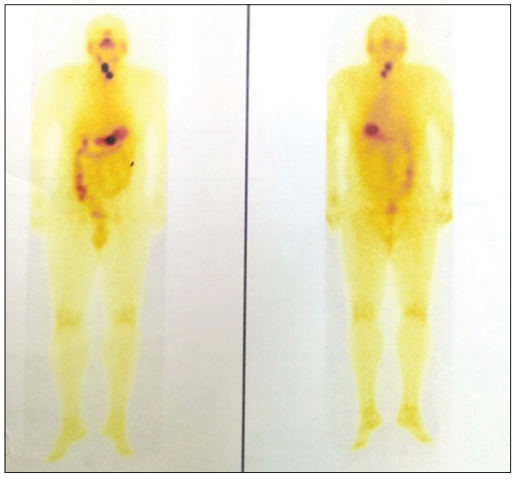

Figure 6: Posttherapy ^{131}I scan showing 2 foci of I-131 uptake in neck

Discussion

The noteworthy aspect in these three cases was that there a rapid progression in the context of low serum Tg level, despite multimodality treatment instituted and early diagnosis. All the cases showed very low stimulated Tg and minimal/absent I-131 uptake in the lesions. This underscored the fact that relying only on conventional tools for disease detection such as ^{131}I scan, stimulated Tg, and local USG was not sufficient to assess the disease burden. A study by Ibrahimpasic *et al*. suggested that PDTCs without any macroscopic disease and undetectable serum Tg levels had a better prognosis.[5] The three cases in our series, had rapid disease progression of the macroscopic disease, consistent with the inherently aggressive nature of PDTCs. An evidence-based review by Sanders *et al*. suggested this subgroup may benefit from aggressive treatment; although, the role of radio-iodine was not conclusive.[1] EBRT is recommended by extrapolating data from well DTC with high-risk features. However, some studies have shown I-131 avid disease, and that radioactive iodine therapy postsurgery is useful, and early diagnosis is essential for PDTC.[8,9] Furthermore, the role of multikinase inhibitors and the appropriate time for their initiation is not clearly defined. From the genomic perspective, BRAF, MAPK, and histone deacetylase (HDA1C) inhibitors may be beneficial for a selective group of patients,[10,11] but need further clinical data for their routine use. Therefore, there is need of such studies to formulate appropriate management of PDTC so as maximize patient benefit.

It is possible that radio-iodine scan positivity and stimulated Tg levels could give a clue about the particular genomic profile of the disease and help in risk-stratification of the PDTCs. Hence, as illustrated and discussed in this communication, PDTCs with minimal/low I-131 avidity and low serum Tg level but with macroscopic disease clinical signs and symptoms of disease progression need close monitoring and other diagnostic modalities including FDG/^{68}Ga-DOTATATE PET-CT and USG, with the development of an appropriate diagnostic and treatment algorithm. Certain other unresolved questions that needs future research direction are: (a) Questionable role of Re-differentiation agents: in one study by Fortunati *et al*., valproic acid induced the expression of NIS and radioiodine uptake in PDTC;[12] (b) histopathology report should include the relative involvement of PDTC areas: A study by Dettmer *et al*. showed that even a small focus of 10% showing poorly differentiated characteristics might result in poor prognosis;[13] (c) defining the role of FDG-PET/CT in PDTC patients, especially for postoperative baseline and follow-up evaluation.

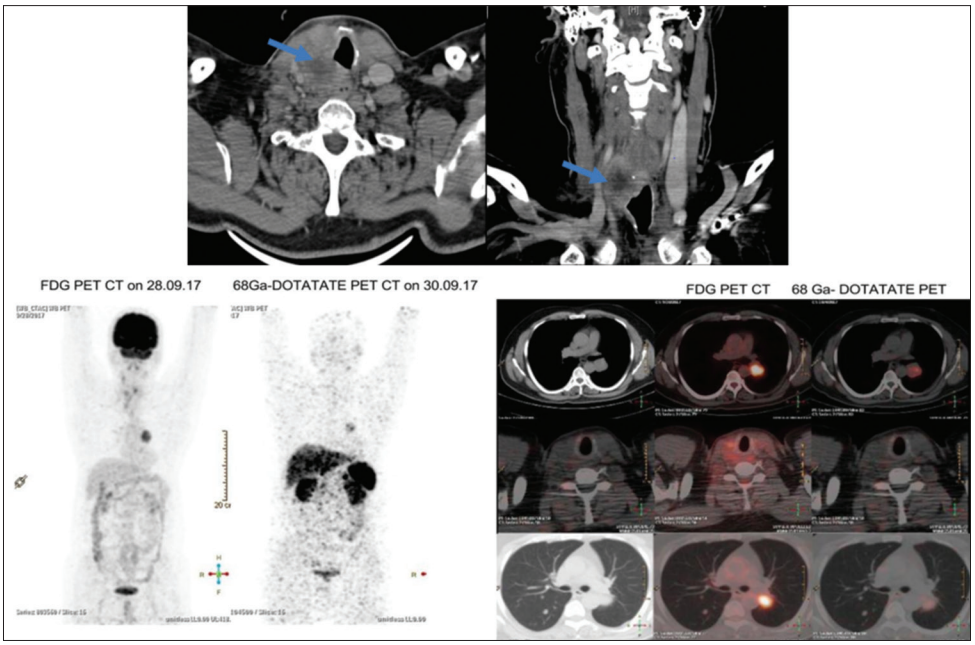

Figure 7: CT scan of mass lesion [Figure 7, upper panel] measuring 4.3 cm × 3.2 cm in right thyroid bed, encasing and infiltrating the trachea; abutting right carotid sheath (blue arrow); enlarged right paratracheal nodes in superior mediastinum ~ 2.8 cm, enlarged left hilar lymph node measuring 1.6 cm. Enlarged right level II and right level III nodes were also noted. fluorodeoxyglucose-positron emission tomography/computed tomography and Ga-68 DOTATATE positron emission tomography/computed tomography MIP images [Figure 7, lower panel right] with metastases. Axial images of positron emission tomography-computed tomography [Figure 7, lower panel, left] showing low grade fluorodeoxyglucose uptake in the infiltrative right paratracheal soft tissue lesion with high fluorodeoxyglucose uptake in the left para-hilar soft tissue lesion. A low grade fluorodeoxyglucose uptake in the right lung nodule is also seen. There is low grade uptake in all lesions on ^{68}Ga-DOTATATE positron emission tomography/computed tomography

Summary/Conclusion/Learning Points

- PDTC constitute the subgroup of thyroid carcinoma with proposed intermediate prognosis (between the well differentiated and anaplastic carcinoma) and whose management is relatively less defined
- Behavioral heterogeneity can be observed within the same histopathological subtype of PDTC with respect to their radioiodine and FDG avidity, and their clinical course and management need to be individualized
- Three clinically challenging and relatively uncommon subset of cases of PDTC is presented with low serum Tg ("nonsecretor") and noniodine concentrating metastatic disease who revealed an aggressive clinical course.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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