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Pakistan Journal of Nuclear Medicine is the official journal of Pakistan Society of Nuclear Medicine

Radioactive iodine uptake in the breast tissue of nulliparous adolescent girls and young women

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ABSTRACT

Background: Pediatric thyroid cancer is the second most common cancer among girls aged 15-19 years, with lymph node involvement and pulmonary metastasis more common than in adults. In interpreting whole-body I-123 scintigraphy, differentiation between physiologic breast uptake and rib or lung metastasis can be challenging. While radioiodine uptake in lactating breasts has been recognized for over 65 years, breast uptake in nulliparous girls and young women has not previously been documented.

Methods: Female nulliparous patients <21 years with primary thyroid cancer requiring whole-body I-123 scintigraphy with anterior and lateral planar images from 25 September 2014 to 22 March 2017 were eligible for inclusion. Four physicians with training in nuclear radiology evaluated the anterior and lateral spot views for the presence of breast activity on a 5-point Likert scale. Fleiss' Kappa and Monte Carlo simulations were used to calculate mean Likert values, reader agreement, and 95% CIs.

Results: For this study, 27 patients met the inclusion criteria (mean age=15.9±2.3 years). Breast activity was present in 20/27 (74%) patients. Mean Likert scores and agreement were: present on frontal images = 3.9 ± 1.2, κ = 0.74 (0.61-0.83); limited to the lower thorax on frontal images = 4.0 ± 1.2, κ = 0.77 (0.63-0.88); present on lateral images = 4.2 ± 1.2, κ = 0.85 (0.71-0.93); and present given all projections = 4.2 ± 1.3, κ = 0.85 (0.71-0.94).

Conclusion: Breast activity on whole-body I-123 scintigraphy is present in the majority of nulliparous young women. However, any suspicious uptake in the chest must be further characterized using lateral views of the chest to differentiate between physiological breast uptake and pathological uptake in ribs or lungs. We recommend routine lateral images of pediatric patients undergoing radioactive iodine scintigraphy for evaluation of thyroid cancer.

Keywords: Breast, lung, metastases, radioiodine uptake, I-123 scintigraphy, thyroid cancer, pediatric.

Received: 01 September 2020

Revised: 02 October 2020

Accepted: 05 October 2020

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Introduction

Pediatric thyroid cancer is increasing in incidence and is now the second most common cancer among girls aged 15-19 years [1], with lymph node involvement and pulmonary metastasis more common than in adults. Whole-body I-123 scintigraphy (I-123 WBS) is recommended by the American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer for risk stratification and treatment planning of intermediate and high-risk patients [2]. It is a well-established diagnostic procedure in the staging of differentiated thyroid cancers, providing valuable information with regard to unanticipated lymph nodes or more distant metastatic disease [3].

In interpreting I-123 WBS, the differentiation between physiologic breast uptake, lung, and osseous metastasis

can be challenging due to considerable overlap in uptake patterns. Accurate disease characterization guides therapeutic strategies and can reduce short and long-term toxicities of unnecessary I-131 treatments, including the potential risk of secondary malignancies [4]. While radioiodine uptake in lactating breasts has been recognized for over 65 years [5-8], breast uptake in nulliparous girls and young women has not been documented in the pediatric population. Therefore, we sought to evaluate the presence of physiologic I-123 breast activity in young nulliparous female patients and explore the utility of obtaining routine lateral views for differentiating physiologic breast uptake from osseous (e.g. rib) and lung metastasis.

Materials and Methods

Patient population

The local Institutional Review Board approved this retrospective HIPAA-compliant study. Inclusion criteria were all nulliparous female patients with known primary thyroid cancer who underwent whole-body I-123 scintigraphy along with lateral spot views of the chest from 25 September 2014 to 23 March 2017. Parous patients and patients whose exams did not include lateral planar images were excluded.

Whole-body imaging

Twenty-four hours following the administration of 5 mCi (185 MBq) of I-123, the scans were obtained using a dual-head large field of view gamma camera and medium-energy general purpose collimator. Anterior/posterior and lateral spot planar images of the chest were obtained at 5 minutes apiece (Figure 1).

Image interpretation

Four pediatric radiologists (10, 8, 7, and 5 years post-fellowship experience) with additional subspecialty training in nuclear radiology evaluated the anterior and lateral scintigraphy images for the presence of breast activity on a 5-point Likert scale (1 = highly unlikely; 5 = highly likely). Whole-body planar images were not evaluated. SPECT/CT, if obtained, was also not evaluated as part of the study. Four findings on planar images were evaluated independently by each of the readers: breast activity 1) present on the frontal images, 2) limited to the lower thorax on frontal images, 3) present in the anterior chest on lateral images, and 4) present given all projections.

Statistical analysis

Demographic information was expressed as mean and standard deviation. Mean Likert values were calculated for each finding. Breast activity was determined to be present if the mean Likert score given all projections was greater than or equal to 4. Interobserver reader agreement on the Likert scale was measured by modified Fleiss' Kappa with weight. A value of 0-0.20 was defined as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1 as almost perfect agreement. 95% confidence intervals were calculated by Monte Carlo simulation. All data analyses were carried out using SPSS Statistics version 21.0 (IBM, New York, NY)

Results

Patient demographics

Twenty-seven studies were carried out from September 2014 to March 2017 on patients who met the inclusion criteria and all 27 patients were included in the study cohort. Patients ranged from 10 to 21 years of age (mean age \pm standard deviation, 15.9 ± 2.3 years). Twenty-six patients had a diagnosis of papillary thyroid cancer and one patient had follicular thyroid cancer. Fifteen out of 27 patients (56%) had received prior I-131 ablation. All patients had thyroid stimulating hormone levels ≥ 30 mU/L and all patients were followed-up clinically for a minimum of 1 year (range: 1.1-3.0 years, mean: 1.8 years) with clinical, biochemical, and/or imaging studies subsequent to whole-body imaging.

Image analysis

Breast activity was present in 20/27 (74%) patients. Modified Fleiss' Kappa analysis demonstrated substantial



Figure 1. I-123 examination in an 18-year-old with papillary thyroid cancer. (a) Anterior and (b) lateral views demonstrate definitive breast uptake (Mean Likert = 5 on both projections).

interobserver agreement on the anterior views and almost perfect agreement on the lateral images (Table 1).

The Likert scores regarding the presence of breast activity was 3.9 ± 1.2 on the anterior images, 4.2 ± 1.2 on the lateral images, and 4.0 ± 1.2 when evaluating for activity limited to the lower thorax on anterior images. The mean Likert score for the overall presence of breast activity when using all projections was 4.2 ± 1.2 . There was no statistically significant difference between anterior and lateral projection Likert scores. When using a mean Likert score of ≥ 4 as the cut-off, the lateral images identified three patients with breast uptake that were otherwise not identified on the anterior images or when evaluating for activity limited to the lower thorax.

Six of the 27 patients (22%) were diagnosed clinically with lung metastases, all based on CT findings. When these studies were retrospectively reviewed, two were categorized as highly likely overall breast uptake (mean Likert score: 4.75 and 5, respectively), two had equivocal breast uptake (mean Likert score: 3.5 for both exams), and two had unlikely breast uptake (mean Likert score: 1.75 and 2, respectively). The remaining 21 patients have no clinical, biochemical, and/or imaging findings to suggest lung metastases.

Discussion

Patterns of radioiodine uptake in lactating breasts have previously been described: full, focal, crescent, and irregular. The causes of these patterns is unclear, but is felt to reflect radioiodine uptake in the collecting duct, breast tissue, or both [8]. In the majority of cases in adults, the uptake is bilateral, but it is usually asymmetric. The pattern of uptake can confidently be recognized as physiologic rather than metastases through recognition of common patterns, particularly bilateral and symmetric, as well as its anteriorly located position in lateral planar imaging, even in the absence of SPECT/CT [9].

Our study examined the presence of radioactive iodine breast uptake in a cohort of nulliparous young female thyroid cancer patients. We found that physiologic breast activity was present in the large majority of patients. Lateral images trended toward higher interobserver agreement and increased confidence in identifying breast activity compared to the anterior view alone. While case reports in the adult literature have described radioiodine uptake in non-lactating breasts [10-12], including in patients with hyperprolactinemia [13, 14] and breast cysts [15], this is the first study to demonstrate radioactive iodine breast activity in a nulliparous pediatric patient population.

In the largest adult study to date, Hammami et al. [16] examined a female cohort of 480 patients with well-differentiated thyroid cancer, four of whom were nulliparous, and concluded that radioiodine breast uptake could be expected in at least 6% of non-breastfeeding hypothyroid female patients with differentiated thyroid cancer. In

comparison, our study found a significantly higher proportion of patients (74%) demonstrating physiologic radioiodine breast uptake. The differences between the two studies can perhaps be accounted for by differences in the patient populations, as the denser breast tissue typically seen in younger patients may result in increased count density and detection. Our study included exams with lateral views, which confirmed breast uptake. Our higher percentage of breast uptake could also be secondary to not having included studies obtained without lateral views, in which uptake may have been attributed to non-breast tissues.

The precise mechanism of iodine uptake in non-lactating breast tissue remains unknown. As iodine uptake in lactating breast tissue is attributed to marked induction of the sodium-iodide symporter in lactating mammary glands [17-19], it stands to reason that hormonal mechanisms resulting in increased expression of the sodium-iodide symporter may play a role in the radioiodine uptake of nulliparous breasts as well. For example, these symporters may be active in nulliparous adolescent girls and young women, and could even demonstrate cyclical changes due to hormonal fluctuation such as during puberty or the menstrual cycle. Although prolactin has been identified as a potential regulator of breast uptake [13], Hammami [16] concluded that prolactin was unlikely to serve a primary role in radioiodine uptake of non-breastfeeding women as prolactin levels were normal in the majority of the patients in that study.

Differentiating physiologic radioiodine breast uptake from rib or lung metastasis is essential in treatment planning. To that end, our study demonstrated a clear trend toward increased confidence and interobserver agreement when using the lateral view to confirm breast uptake compared to the anterior view alone (Figure 2). Three additional patients were classified as having breast uptake when both frontal and lateral views were interpreted compared to the anterior projection alone. As obtaining a lateral view takes only a few additional minutes, we recommend routinely acquiring a lateral projection on all female patients with suspicious uptake in the chest.

There are several limitations to this study. No histologic gold standard was available to confirm that the activity identified as physiologic breast uptake was in fact not lung disease. Although SPECT/CT can provide additional information in relation to planar images regarding localization, characterization, and differentiation of physiologic uptake versus metastatic disease, these images, if obtained, were not used to confirm physiologic breast uptake. Due to additional radiation, SPECT/CT is not routinely carried out in pediatric patients with thyroid cancer but reserved for patients with suspicious activity on planar images or in follow-up of known disease [2, 20-22]. However, four of the six patients (67%) with metastatic lung disease were categorized as having unlikely or equivocal breast activity,

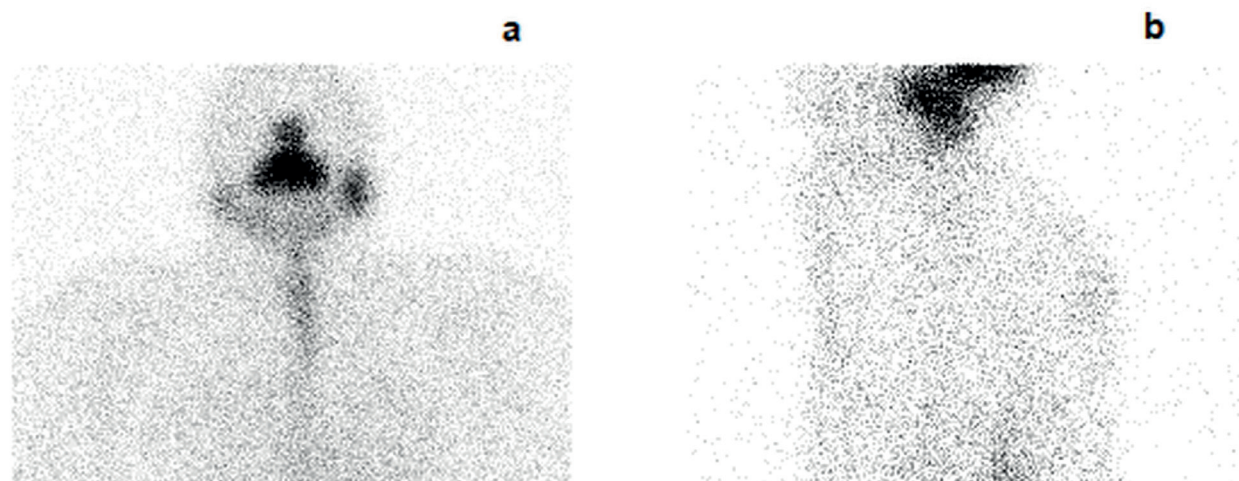


Figure 2. I-123 examination in a 16-year-old with papillary thyroid cancer. (a) Anterior and (b) lateral views demonstrate questionable breast uptake on the frontal image (Mean Likert = 2.75) compared to more definitive uptake on the lateral image (Mean Likert = 4.25).

indicating that the known lung disease was not incorrectly attributed to breast activity. Of the remaining 21 patients with no evidence of lung metastasis during follow-up, 19 of the 21 (90%) showed likely or highly likely breast uptake. Another limitation is that hormonal levels, specifically prolactin, were not routinely drawn on patients to exclude the possibility of prolactinemia, a known cause of breast uptake. Medications such as antipsychotics, tricyclic antidepressants, antihypertensives, and opiates are known to increase serum prolactin levels and could thus increase breast uptake, but no drug histories were obtained [23]. However, no patients had clinical evidence of hyperprolactinemia. Finally, due to the homogenous patient population (26 patients with papillary thyroid cancer compared to one follicular cancer), there may be a potential bias to under-call lung metastasis due to the relatively low pre-test probability. However, all readers were blinded to the subtype of thyroid cancer the patient was diagnosed with and thus this should not have affected interpretation.

Conclusion

Our study documents that breast activity on whole-body I-123 scintigraphy is present in the majority of nulliparous young women. However, any suspicious uptake must be further characterized using lateral views of chest to differentiate between physiological breast uptake or pathological uptake in lungs or ribs. Routine use of lateral images of pediatric patients undergoing radioactive iodine scintigraphy for evaluation of thyroid cancer is thus recommended. The etiology of physiologic breast uptake in nulliparous/pediatric women remains unknown, perhaps involving physiologic upregulation of the sodium-iodide symporter, and is a potential direction of future research.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures carried out in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of retrospective study, formal ethical approval is not required.

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