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Review Article

Breast Uptake of Radio-iodine in Differentiated Thyroid Cancer

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ABSTRACT

Radioiodine is often seen to accumulate within breast tissue in patients with differentiated thyroid cancer. Although the risk of secondary breast malignancy in patients with differentiated thyroid cancer treated with radioiodine is controversial, the identification and reduction of this uptake is prudent to minimize the radiation absorbed dose to the breast tissue. This article reviews the literature describing the etiology, frequency and patterns of radioiodine uptake in breast tissue. Approaches and techniques to help minimize the radioiodine uptake in lactating and nonlactating breasts are presented.

Introduction

Radioiodine uptake in the breasts is frequently seen in radioiodine scanning done before and after radioiodine therapy for differentiated thyroid cancer. This article reviews the relevant literature regarding radioiodine activity within breasts, the cause and potential management of this uptake in patients with differentiated thyroid cancer. Despite the controversy regarding the increased risk of breast cancer related to radioiodine therapy, the uptake of radioiodine in the breasts is undesirable and must be minimized if possible, to reduce radiation exposure to the breasts. With a thorough understanding of the frequency, patterns, etiology, and mechanism of radioiodine breast uptake as well as the techniques to potentially reduce radioiodine uptake in the breast, the nuclear medicine physician, nuclear radiologist or endocrinologist can help decrease or even eliminate the uptake of radioiodine in the breast. This is turn may potentially reduce the radiation absorbed dose to the breast from 131-I therapies.

I Etiology of Radioiodine Uptake in Breasts

I-131 is used as a standard method of diagnosis and treatment for differentiated thyroid cancer. Multiple entities associated with breast uptake of radioiodine have been reported and include lactating breasts, hyperprolactinemia related conditions, localized pathologies like breast carcinoma, fibroadenomas, lactating breast with galactorrhea, mastitis and rarely metastatic disease to the breast from other malignancy such as thyroid carcinoma [1-16]. At times contamination, rib, lung, liver, soft tissue uptake and/or blood pool may at times be mistaken as breast activity [17].

i Sodium Iodide Symporter

The mechanism(s) of breast uptake of radioiodine has not been extensively evaluated. Sodium-iodide symporter (NIS) mediates uptake within thyroid gland and thyroid cancer. Similar expression has been demonstrated in extrathyroidal tissues and these organs are often seen as demonstrating physiological uptake within the radiodine scans. The normal human female breast epithelium expresses the sodium iodide symporter and can also organify iodide [18-20]. Over expression of Na-I symporter during lactation or in malignant conditions such as thyroid and breast cancer may be one of the most important mechanism of radioiodine uptake within the breasts. [5-9, 12, 21-24].

ii Prolactin

Some authors proposed the role of prolactin (PRL) causing iodine uptake within the human mammary cells. Barzowska suggested role of prolactin in radioiodine uptake in the lactation period [16]. PRL receptors are

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demonstrated in breast tissue and hyperprolactinemia had been proposed in some case reports even in nonlactating breasts [6, 25]. Animal studies have shown that PRL stimulation upregulates the expression of NIS (at both the mRNA and protein levels) in the normal lactating mammary gland, rendering these tissues capable of concentrating radioiodine. Expression of Na-I symporter may demonstrate cyclical changes and has been reported within the breast as a result of hormonal fluctuations and lactation as proposed by some authors[11, 12, 25, 26].

Ronga showed uptake of iodine in postmenopausal breast tissue in 2 patients with hyperprolactinemia [6]. The breast uptake was correlated to the high prolactin levels in both cases. In a previous study of 302 patients who underwent 131I WBS following radioiodine ablation of papillary or follicular thyroid carcinomas, breast tissue uptake was evident in only 4 cases [22]. One of the four patients had galactorrhea, and another had previously been treated with the antidopaminergic drug, sulpiride.

II Frequency and Pattern of Uptake

The literature reporting radioiodine uptake largely consists of case reports and case series and the frequency has not well reported. In a study of 302 patients who underwent 131I. WBS following radioiodine ablation of papillary or follicular thyroid carcinomas, breast tissue uptake was evident in only 4 cases [22]. Recently, Van Nostrand *et al.* reported that radioiodine administered for a whole-body scan in patients with well-differentiated thyroid cancer (WDTC) may localize in breast tissue in as many as 6% of patients, and this raises the possibility of delivering a significant, unintended radiation absorbed dose to breast tissue [27]. This was also previously reported by Hammami *et al.* [2].

Various patterns of breast uptake have been described, mainly categorized focal or diffuse dependent on the etiology. Focal or irregular or crescentic pattern of breast uptake is identified in localized breast pathology like breast carcinoma, fibroadenoma, fibrous dysplasia, lactating breasts, metastatic disease to the breast from other malignancy such as thyroid carcinoma. Diffuse pattern of breast uptake is identified in more global hormonal stimulation like lactating breast with galactorrhoea, hyperprolactinemia related conditions.

Bakheet and Hammani have described four patterns of uptake in postpartum breasts in twenty female patients one week after they stopped breast feeding: 'full', 'focal', 'crescent' and 'irregular' [2]. The full pattern represents diffuse intense uptake over the entire breast. Central, subareolar uptake gives a focal pattern of uptake, whereas more intense peripheral uptake represents a crescent. The fourth refers to irregular pattern of uptake and can mimic metastases. Thus, while full bilateral uptake is typically physiological, unilateral or irregular uptake was suggested to be highly suspicious for malignancy. Lactation usually causes uptake in bilateral breasts. Preferential lactation from one breast is a common occurrence among breast feeding mothers [26]. However, it can give rise to highly unusual and suspicious imaging appearances. In this case, unilateral uptake of I-131 was present in the right breast only as the patient had preferentially lactated only from the right side.

III Approach to Imaging

Diagnostic radioiodine imaging prior to ablative therapy may be of value in determining which patients may demonstrate excessive breast uptake of I-131 if radioiodine therapy is contemplated. The breast uptake can easily be distinguished by lateral images in most cases. In some instances, SPECT-CT may be used for confirming breast uptake at times particularly when diffuse to distinguish the uptake to be localized to lungs.

Barazowska demonstrated the utility of pretherapy imaging prior to radioiodine therapy and recommended I-123 as agent of choice for imaging [16]. In this study, a series of post-partum patients were imaged at varying time points postpartum, some using lactation inhibiting agents and I-123 scans were used to assess breast uptake. In the group with use of lactation inhibiting agents like bromocriptine or cabergoline, there was absent uptake as early as 3 weeks with their use and no patients demonstrated uptake beyond 14 weeks of their use. On the other hand, the 3 patients with no use, uptake was demonstrated as late as 32 weeks. No significant uptake was noted in one patient who did not initiate breast feeding. The author favored use of cabergoline over bromocriptine in suppressing breast activity. Another case report by Hsiao *et al.* documented the utility of radioiodine scan assessing for breast uptake prior to I-131 therapy to potentially prevent unnecessary radiation exposure to the breasts [3].

IV Proposed Management of Radioiodine Uptake

Some of the interventions are based on identifying the pattern and probable etiology for breast uptake. This would be as follows:

i If There is Diffuse Bilateral Breast Uptake

Evaluate for etiologies such as hyperprolactinemia, and lactation by gathering adequate clinical history.

ii Diffuse Unilateral Breast Uptake

Evaluate for clinical history related to mastitis with serosanguinous discharge or contamination. Preferential lactation history from that breast and mammogram information will be helpful.

iii Focal, Irregular or Crescentic Patterns of Bilateral Breast Uptake

Evaluate for benign breast conditions such as fibroadenoma, fibrous dysplasia or in some situations lobular pattern of uptake in lactation. Breast uptake related to primary breast malignancy or metastatic breast involvement from thyroid malignancy are possible bur rare.

V Approaches to Reduce Breast Uptake

Until further studies with a large patient numbers to evaluate the risk of breast malignancy from radiation exposure are performed, we believe that it is logical and prudent to identify and attempt to reduce radioiodine uptake in breast tissue observed on any pre-treatment radioiodine scan in order to limit the radiation absorbed dose to the breasts from any planned 131-I treatment. Unfortunately, there is little data in the

literature regarding how the radioiodine breast uptake should be managed, and as a result, there has been no consistent management of this radioiodine breast uptake among our nuclear medicine physicians and endocrinologists. Each team of the interpreting nuclear medicine physician and endocrinologist have managed the patients independently, and the approaches have included (1) cancellation of the I-131 therapy, (2) postponement of the I-131 therapy for several months with or without repeat radioiodine scan before subsequent I-131 therapy, (3) postponement of I-131 treatment with repeat radioiodine scan of the breast performed during a different time of the menstrual period than when the first scan was performed, (4) postponement of the I-131 treatment with subsequent treatment with lactation inhibiting drugs such as cabergoline or (5) proceeding with the planned I-131 despite the significant uptake.

The approaches that have been used in attempts to decrease radioiodine uptake in breast tissue prior to 131-I therapy in our institution are several:

a. In lactating breast/postpartum conditions.

The approaches that have been used in attempts to decrease radioiodine uptake in breast tissue prior to 131-I therapy in our institution are several:

- In postpartum patients, wait for 3-6 months, and re-image with 123-I;
- Administer cabergoline 0.25 mg twice a week up to 1 mg twice a week for approximately 4 weeks based on prolactin level, and re-image with 123-I;
- Administer bromocriptine 7.5 mg twice a day for approximately 4 weeks and re-image.

b. Similarly, in a nonlactating non postpartum breast, we recommend treatment with cabergoline for 3-4 weeks and reevaluate with iodine scanning and proceeding with therapy. We may escalate the dose to achieve more suppression of breast uptake if adequate suppression is not achieved.

c. In cases of no definitive cause, either a trial of cabergoline or bromocriptine. Alternatively, no drug intervention and perform repeat imaging with 123-I in a different phase of menstrual cycle or 3-6 months later.

Summary

With a thorough understanding of the frequency, patterns, etiology, and mechanism of radioiodine breast uptake as well as the techniques to reduce false positive uptake and potentially reduce radioiodine uptake in the breast, the nuclear medicine physician, nuclear radiologist or endocrinologist can help decrease or even eliminate the uptake of radioiodine in the breast. This is turn may potentially reduce the radiation absorbed dose to the breast from 131-I therapies. Despite the controversy regarding the increased risk of breast cancer related to radioiodine therapy, the uptake of radioiodine in the breasts is undesirable and must be minimized if possible, to reduce radiation exposure to the breasts.

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