Nasal Symptoms After Radioiodine Therapy: A Rarely Described Side Effect with Similar Frequency to Lacrimal Dysfunction

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Background: Salivary and lacrimal side effects of radioiodine therapy have been carefully described. However, nasal side effects are rarely described. The objective of this study was to document the frequency of nasal side effects in comparison to the already well-documented lacrimal side effects and to determine contributing risk factors.

Methods: A retrospective review of the medical records of 807 patients with differentiated thyroid cancer who received care at an academic medical center was conducted. Four hundred eleven patients who received treatment with radioactive iodine (RAI) were identified and included in the analysis. The frequency of both nasal and lacrimal side effects was ascertained. Factors that may have contributed to patients sustaining nasal damage after RAI therapy were also documented. These factors included radioactive iodine dose, method of preparation for receiving RAI therapy, and patient characteristics.

Results: The mean dose of RAI administered was 109 mCi. Forty-three patients (10.5%) and 40 patients (9.7%) developed nasal and lacrimal side effects, respectively, following RAI treatment. The mean time of onset of nasal symptoms was 11 days, compared with 10 months for lacrimal symptoms. Radioiodine dose and body mass index were significantly positively and negatively correlated, respectively, with sustaining nasal side effects (p values of 0.04 and 0.01, respectively). Similarly, both RAI dose and body mass index were significantly correlated, positively and negatively, respectively, with sustaining lacrimal side effects (p values of 0.02 and 0.01). Preparation for treatment using a withdrawal protocol was associated with increased risk of both nasal and lacrimal side effects, compared with a recombinant human thyrotropin (rhTSH) protocol (p values of <0.01 and 0.01). The odds ratios (95% confidence interval [CI]) for nasal and lacrimal side effects with recombinant rhTSH preparation were 0.22 [0.11–0.44] and 0.37 [0.18–0.76], respectively. Instructions to maintain adequate hydration and development of lacrimal symptoms were only associated with nasal symptoms in unadjusted analyses.

Conclusions: Both nasal and lacrimal dysfunction occurred at an approximately 10% frequency. Although it cannot be determined whether acute nasal side effects are followed by long-term ramifications, these consequences of RAI could potentially add to the reasons to carefully evaluate the benefits and risks of RAI therapy on an individual basis.

Introduction

DESPITE THE PROVEN EFFICACY of radioactive iodine (RAI) in the treatment of thyroid cancer, there are several serious side effects associated with its use (1). These side effects, which are due to the impact of RAI on nonthyroid tissue, are one of the major causes of morbidity in thyroid cancer survivors (1). Salivary gland dysfunction has been well described and can be manifest as sialadenitis, xerostomia, taste alterations, hypogeusia, and sialolithiasis (2,3).

Another organ system recently recognized to be affected by RAI is the lacrimal system. Radioactivity has been demonstrated in tears (4) and contact lenses (5) after RAI ad-

ministration. Lacrimal dysfunction is manifest as epiphora, tearing, xerophthalmia, and recurrent or chronic conjunctivitis. These complications of RAI therapy are being increasingly recognized in case reports (6,7). Conjunctivitis was a complaint expressed by 23% of patients in one study in which RAI was given in a cumulative fashion with resultant administration of doses as high as 1000 mCi (8). In overlapping cohorts, significant tearing was documented in 10 of 390 (2.6%) (7) and 26 of 563 (4.6%) (9) patients following RAI therapy. Lacrimal dysfunction described as “watery eyes” occurred in 10% of patients in a recent trial, even though RAI doses of 30–100 mCi were used (10). Xerophthalmia and abnormal lacrimal function tests were noted

in 18% (2) and 92% (11) of patients respectively after RAI therapy. Abnormalities associated with these symptoms include nasolacrimal duct obstruction, common canaliculus obstruction, and distal upper and lower canaliculi obstruction.

The author has encountered a subset of patients who complain of nasal symptoms shortly after RAI therapy. These symptoms include nasal pain, nasal sores, nasal dryness, blood clots in the nose, and epistaxis. RAI concentration in the area of the nose has been reported after a 5 mCi diagnostic dose of RAI (12). Concentration of RAI within the nose after a therapeutic dose of 150 mCi, accompanied by the patient experiencing epistaxis, has also been reported (13). A retrospective review of patients undergoing diagnostic scintigraphy with 5 mCi showed that the nose was a common site of RAI accumulation (14). In fact, nasal uptake was demonstrated in 95% of patients. There was a round pattern of distribution in 75% of patients, with linear or oblong patterns of distribution being less common. In a review of 15 RAI therapies in 10 patients receiving RAI doses of 51–450 mCi, two cases of nasal complaints were encountered (15). These complaints occurred 1–2 weeks after therapy and were resolved by 3 months. In all these reports, the patients were hypothyroid at the time nasal accumulation of RAI was documented.

The author postulated that nasal symptoms occur in a significant number of patients, but either they are not reported by the patient or they are not recognized by the physician as being related to RAI. The intent of this study was to perform a retrospective chart review to document the frequency of nasal symptoms after RAI administration. It was hypothesized that nasal symptoms would be documented in about 10% of patients. As lacrimal symptoms have already been well documented, albeit with widely varying frequencies of between 2.6% and 92% (2,7–11), lacrimal symptoms were simultaneously documented as a means of validating the ability to detect known side effects. It was postulated that lacrimal symptoms would be documented in approximately 20% of patients.

Methods

Index case and chart review

The index case that prompted this study is described. A retrospective review of patients with a diagnosis of thyroid cancer (ICD-9 193) from 2008 onwards was then performed following Institutional Review Board approval. Medical records of patients documented to have received an initial RAI therapy were reviewed for a diagnosis of epiphora (ICD-9 375.20), other lacrimal dysfunction (ICD-9 375.0–375.9), epistaxis (ICD-9 784.7), or other nasal problems (ICD-9 478.19) that were newly documented following the date that RAI therapy was administered. Potentially related diagnoses such as conjunctivitis, sinusitis, or sinus complaints (as described by the index case) were also sought. The texts of the medical records were also reviewed further to identify any specific complaints not reflected in the diagnostic codes (e.g., dry eyes, excessive tearing, nasal pain, dry nose, nasal bleeding, blood clots in nasal discharge). In patients found to have either lacrimal or nasal diagnoses or complaints, other factors that may have contributed to their sustaining damage after RAI therapy were also documented. These included RAI dose, method of preparation for receiving RAI therapy

(hypothyroid state versus recombinant human thyrotropin [rhTSH] administration), patient sex, patient age, patient weight, patient body mass index (BMI), factors potentially underlying lacrimal or nasal dysfunction (external beam radiation to the neck or autoimmune disease), and medications (anticholinergic drugs or drugs causing hypotension or dehydration).

If available, patient instructions at the time of RAI administration were also reviewed to determine if the patient was told to pursue additional hydration and/or use sialogogues. For many patients the instructions given regarding hydration or sialogogue use could not be discerned from chart review. The timing of the lacrimal or nasal symptoms with respect to the patient's RAI dose was also documented. The subset of patients with thyroid cancer who were documented to have received therapeutic doses of RAI served as the denominator for the study. The percentage of these patients who were given diagnoses of lacrimal or nasal dysfunction was combined with the percentage of patients who appeared to have developed lacrimal or nasal symptoms after RAI, and this combined number was documented. In addition, as a pilot or preliminary analysis, the factors (e.g., RAI dose, patient sex) that appeared to be associated with developing lacrimal or nasal symptoms were reported.

Statistical analysis

Baseline characteristics of the study population were calculated. Characteristics of the participants were reported as mean (standard deviation) for continuous variables and frequency (proportion) for the categorical variables. Spearman correlation coefficients were used to assess the correlation between the presence or absence of lacrimal or nasal side effects and continuous variables such as patient age and RAI dose. A p value of <0.05 was interpreted as indicating a significant association between the occurrence of side effects and the continuous variable (e.g., advancing age). Odds ratios for lacrimal and nasal side effects based on the categorical variables such as female versus male, rhTSH preparation versus withdrawal preparation for RAI therapy, and so forth, were also calculated. The odds ratio and its 95% confidence interval [CI] were initially calculated using the method described by Altman (16); p values were calculated using Fisher's exact test. An odds ratio of less than 1 (with a CI not including 1) for rhTSH preparation versus withdrawal preparation, for example, was interpreted as indicating a greater risk of side effects being sustained with a withdrawal method of preparation.

Additionally, multivariable logistic regression modeling was also performed to assess the impact of the various parameters on the likelihood of sustaining lacrimal and salivary side effects by calculating unadjusted and adjusted odds ratios. Adjustment for multiplicity was performed with use of a Bonferroni correction. In addition, adjustment was also made for the shared variation between the variables (e.g., between body weight and BMI, and between these variables and sex).

Results

Index case

A 59-year-old woman was treated with 150 mCi (5.5 GBq) of RAI for a T3 multifocal papillary thyroid cancer with

extensive cervical lymph node involvement. The patient was healthy without any diagnoses, other than thyroid cancer. Her only medications were levothyroxine and cholecalciferol. The latter medication had been advised for skeletal benefits. Her baseline serum TSH while taking levothyroxine was 0.2 mIU/L. She was prepared for treatment using a low iodine diet of 2 weeks' duration and rhTSH injections. The post-therapy whole-body scan of the patient is shown in Fig. 1. The accumulation of radiotracer within the nasal area is clearly visible. The patient maintained an increased level of hydration for 48 hours after her RAI therapy and also consumed lemon candy frequently for 24 hours. She had no immediate symptoms following her therapy. Approximately 10 days after her therapy, she developed nasal tenderness and bloody nasal discharge. She consulted her primary care physician who suspected a sinus infection and prescribed antibiotics. The patient had two episodes of epistaxis over the following week. She then had residual symptoms of "crusting" and dryness in the nose for an additional 2 weeks. These symptoms also resolved and the patient experienced no further nasal symptoms. She did not notice any decrement in her sense of smell. She had no salivary symptoms during this time. When last seen 9 months after her initial RAI therapy she had not experienced any lacrimal symptoms.

Chart review

Eight hundred seven cases of thyroid cancer diagnosed at Georgetown University between 2008 and 2012 were identified by searching the electronic medical record system. It was possible to determine that 411 of these patients had received RAI therapy, with specific details concerning their therapy (RAI dose and method of preparation) also being available. Most patients in the first half of this time period were admitted to the hospital for a 24-hour period after their

therapy; most patients in the latter half of this time period were treated as outpatients. The RAI-treated patients served as the cohort for further investigation. The remaining patients either did not receive RAI therapy, were not documented to have received RAI, or had insufficient documentation to determine their dose and preparation method. New diagnoses of epiphora or other lacrimal dysfunction were identified in 17 patients (4.1%). New diagnoses of epistaxis or other nasal problems were identified in 15 patients (3.7%). The office visits of the 411 patients were reviewed for mention of potential ophthalmologic complaints such as dry eyes, tearing, overflowing tears, eye pain, and so forth. The visits were also reviewed for mention of new potential nasal complaints such as nasal pain, nasal sores, nasal tenderness, bloody nasal discharge, dry nose, and so forth. With inclusion of these complaints, the number of additional patients who appeared to have sustained lacrimal or nasal damage was 23 (5.6%) and 28 (6.8%), respectively. The list of signs and symptoms that captured the remaining affected patients not already identified by diagnostic codes are shown in Table 1. Based on the

TABLE 1. SIGNS, SYMPTOMS, AND PRACTICES USED TO IDENTIFY PATIENTS WITH SIDE EFFECTS FROM RADIOACTIVE IODINE

Lacrimal side effects

Symptoms reported in the patient chart

- Feeling of generalized discomfort in eyes
- Feeling of dry eyes
- Feeling that the eyes are irritated
- Feeling of pressure in eyes
- Pain in the eyes
- Red eyes
- Intolerance of wearing contact lenses
- Frequent tearing
- Overflowing tears
- Excessive tearing in dry or cold environments
- Diagnosis of conjunctivitis
- Recurrent conjunctivitis
- Chronic conjunctivitis

Practices documented in the patient's chart

- Use of artificial tears or other lubricants
- Use of tissue paper to wipe tears
- Use a vaporizer or humidifier in the home or at work to relieve eye symptoms

Nasal side effects

Symptoms reported in the patient chart

- Feeling of generalized nasal discomfort
- Feeling of a dry nose
- Feeling that the nose is irritated
- Feeling of a hot or burning nose
- Feeling that the surface inside the nose is cracking
- Crusting in the nose
- Pain or sores in the nose
- Noticed blood on tissue paper
- Experienced nasal discharge
- Experienced nose bleeds
- Noticed an altered sense of smell

Practices documented in the patient's chart

- Use saline nasal sprays
- Use of ointments/lubricants in the nose
- Use a vaporizer or humidifier in the home or at work to relieve nasal symptoms
- Use of nasal rinses

FIG. 1. Post-therapy radioiodine scan of index patient.

combination of diagnostic codes and patient complaints, 40 patients (9.7%) and 43 patients (10.5%) were deemed to have suffered lacrimal and nasal side effects from their RAI treatment. Twenty-three (5.6%) patients experienced both lacrimal and nasal symptoms.

Table 2 shows the characteristics of the patients in the study. Table 3 shows the prognostic features of their thyroid cancer and details of their RAI treatment. Most patients had a diagnosis of papillary thyroid cancer and had stage 1 or 2 disease. Less than 1% (0.9%) of the cohort had a documented diagnosis of hypoparathyroidism. Most patients were treated following preparation with rhTSH. The mean dose of RAI administered was 109 mCi (4.04 GBq). A random sample of 20 posttherapy scans from the latter period of the study when digital images were available showed that RAI uptake above background activity could be visualized in the nasal area in 80% of scans. The mean time of onset of lacrimal symptoms in those who experienced them was 10 months (SD 37 days). The mean time of onset of nasal symptoms in those who experienced them was 11 days (SD 9 days). No patients could be identified who were still suffering from nasal symptoms during a 3- to 12-month follow-up period.

Tables 4–7 document the variables associated with developing side effects after RAI treatment. Among the continuous variables, BMI was significantly negatively correlated and RAI dose was significantly positively correlated with sustaining lacrimal and nasal side effects (Table 4). The percentage of patients with side effects increased with the magnitude of the RAI dose (see Table 5), with a

TABLE 2. CHARACTERISTICS OF STUDY PARTICIPANTS (N=411)

<i>Characteristic</i>	
Continuous variables, mean (SD)	
Age, years	47.8 (16.9)
Weight, kg	80.1 (15.7)
BMI, kg/m ²	27.1 (5.3)
Categorical variables, n (%)	
Sex	
Female	326 (79.3)
Male	85 (20.7)
Menopausal status	
Premenopausal	156 (38.0)
Postmenopausal	170 (41.3)
N/A	85 (20.7)
Coexistent Hashimoto's	
No	337 (82.0)
Yes	74 (18.0)
Coexistent Sjögren's syndrome	
No	401 (97.6)
Yes	10 (2.4)
Coexistent external beam radiation therapy	
No	399 (97.1)
Yes	12 (2.9)
Use of anticholinergic medication	
No	404 (98.3)
Yes	7 (1.7)
Use of antihypertensive medications	
No	321 (78.1)
Yes	90 (21.9)

SD, standard deviation; BMI, body mass index.

TABLE 3. PARAMETERS RELATED TO DIFFERENTIATED THYROID CANCER AND RADIOIODINE TREATMENT

Thyroid cancer-related parameters

Characteristic, n (%)	
Type of differentiated thyroid cancer (DTC)	
Papillary thyroid cancer	339 (82.5)
Follicular variant of papillary thyroid cancer	45 (10.9)
Follicular thyroid cancer	27 (6.6)
Multifocal	
Yes	222 (54.0)
No	189 (46.0)
Cervical node involvement	
Yes	219 (53.3)
No	192 (46.7)
Capsular or vascular invasion	
Yes	157 (38.2)
No	254 (61.8)
Extrathyroidal extension	
Yes	80 (19.5)
No	331 (80.5)
Distant metastases	
Yes	25 (6.1)
No	386 (93.9)
DTC stage (TNM)	
1	168 (40.9)
2	123 (29.9)
3	115 (28.0)
4	5 (1.2)

Radioiodine-related parameters

Continuous variables, mean (SD)	
Radioiodine dose, mCi	109 (43)
Radioiodine dose, GBq	4.03 (1.59)
TSH value for withdrawal patients, mIU/L	80 (37)
Categorical variables, n (%)	
Method of TSH elevation	
rhTSH	342 (83.2)
Withdrawal	69 (16.8)
Instructed to use lemon candy	
Yes	183 (44.5)
No	76 (18.5)
Not documented (instructions not documented in chart)	152 (37.0)
Instructed to maintain additional hydration	
Yes	212 (51.6)
No	14 (3.4)
Not documented (instructions not documented in chart)	185 (45.0)

TSH, thyrotropin; rhTSH, recombinant human thyrotropin.

TABLE 4. ASSOCIATION OF CONTINUOUS VARIABLES WITH DEVELOPING SIDE EFFECTS AFTER RADIOIODINE TREATMENT

	<i>Lacrimal side effects</i>		<i>Nasal side effects</i>	
<i>Continuous variables</i>	<i>Spearman correlation</i>	<i>p Value</i>	<i>Spearman correlation</i>	<i>p Value</i>
Age, years	0.41	0.31	0.48	0.22
Weight, kg	−0.66	0.05	−0.62	0.09
BMI, kg/m ²	−0.73	0.02	−0.77	0.01
RAI dose, mCi	0.86	0.01	0.67	0.04

RAI, radioactive iodine.

TABLE 5. ASSOCIATION OF RADIOACTIVE IODINE DOSE TERTILES WITH LACRIMAL AND NASAL SIDE EFFECTS AFTER RADIOIODINE TREATMENT

<i>RAI tertile</i>	<i>N in tertile (median, min-max values)</i>	<i>Patients with lacrimal side effects (n=40)</i>	<i>Patients with nasal side effects (n=43)</i>
Tertile 1	99 (30, 30–80)	1 (1%)	5 (5%)
Tertile 2	180 (100, 81–100)	12 (6.7%)	16 (8.9%)
Tertile 3	132 (150, 101–180)	27 (20.5%)	22 (16.7%)
<i>p</i> Value for trend		0.01	0.03

significant association between increasing dose and increasing percentage of both lacrimal and nasal side effects. Among the categorical variables, being prepared for treatment using a withdrawal protocol was associated with increased risk of both lacrimal and nasal side effects (see Tables 6 and 7, respectively). Not being instructed to maintain additional hydration was associated with developing nasal side effects. In addition, postmenopausal status and coexisting Hashimoto's were both associated with a trend towards both increased lacrimal and nasal side effects. There was a high likelihood of patients with lacrimal side effects sustaining nasal side effects also (Table 7).

In multivariable logistic regression analysis only three variables remained significantly associated with the side effects reported by patients. Lacrimal side effects were negatively associated with BMI ($p=0.02$), positively associated with RAI dose ($p=0.01$) and were less likely with rhTSH preparation ($p=0.01$). Similarly, nasal side effects were

negatively associated with BMI ($p=0.01$), positively associated with RAI dose ($p=0.04$) and were less likely with rhTSH preparation ($p<0.01$). There was no longer an association between lacrimal side effects and experiencing nasal side effects when other variables were included in the model.

Discussion

The percentage of patients who had sustained lacrimal or nasal symptoms following RAI therapy was at the lower end of the anticipated range. However, given that this is a retrospective study, the frequency of these side effects is likely to be significantly underreported. It is interesting that relevant diagnoses were only recorded in the medical charts of about half of the identified patients, and that specifically searching the text of the patients' clinical encounters was needed to identify the additional half of the cases. The findings from this retrospective study can hopefully be used to guide future

TABLE 6. ASSOCIATION OF CATEGORICAL VARIABLES WITH LACRIMAL SIDE EFFECTS AFTER RADIOIODINE TREATMENT

<i>Categorical variables</i>	<i>Lacrimal side effects</i>	<i>No lacrimal side effects</i>	<i>Odds ratio [CI]^a</i>	<i>p Value</i>
Sex				
Female (n=326)	32	294	1.04 [0.46–2.36]	0.9
Male (n=85)	8	77		
Preparation method				
rhTSH (n=342)	27	315	0.37 [0.18–0.76]	0.0067
Withdrawal (n=69)	13	56		
Instructed to use lemon candy				
Yes (n=183)	17	166	1.01 [0.40–2.54]	0.98
No (n=76)	7	69		
Not documented (n=152)	16	136		
Instructed to maintain hydration				
Yes (n=212)	19	193	0.36 [0.09–1.41]	0.14
No (n=14)	3	11		
Not documented (n=185)	18	167		
Menopausal status				
Premenopausal (n=156)	11	145	0.51 [0.24–1.09]	0.08
Postmenopausal (n=170)	22	148		
N/A (n=85)	7	78		
Coexistent Hashimoto's				
No (n=337)	29	308	0.54 [0.26–1.14]	0.10
Yes (n=74)	11	63		
Use of antihypertensive medications				
No (n=321)	31	290	0.96 [0.44–2.10]	0.92
Yes (n=90)	9	81		

^aOdds ratio is for risk of lacrimal side effects in females compared with males, rhTSH preparation versus withdrawal preparation, use of lemon candy versus no use, and so forth.

CI, 95% confidence interval.

TABLE 7. ASSOCIATION OF CATEGORICAL VARIABLES WITH NASAL SIDE EFFECTS AFTER RADIOIODINE TREATMENT

<i>Categorical variables</i>	<i>Nasal side effects</i>	<i>No nasal side effects</i>	<i>Odds ratio [CI]^a</i>	<i>p Value</i>
Sex				
Female (<i>n</i> =326)	34	292	0.98 [0.45–2.14]	0.97
Male (<i>n</i> =85)	9	76		
Preparation method				
rhTSH (<i>n</i> =342)	25	317	0.22 [0.11–0.44]	<0.01
Withdrawal (<i>n</i> =69)	18	51		
Lacrimal side effects also				
Lacrimal side effects (<i>n</i> =40)	23	17	23.71 [10.97–51.39]	<0.01
No lacrimal side effects (<i>n</i> =371)	20	351		
Instructed to use lemon candy				
Yes (<i>n</i> =183)	19	164	0.88 [0.38–2.03]	0.97
No (<i>n</i> =76)	9	68		
Not documented (<i>n</i> =152)	14	136		
Instructed to maintain hydration				
Yes (<i>n</i> =212)	20	192	0.26 [0.08–0.91]	0.04
No (<i>n</i> =14)	4	10		
Not documented (<i>n</i> =185)	19	166		
Menopausal status				
Premenopausal (<i>n</i> =156)	11	145	0.49 [0.23–1.03]	0.06
Postmenopausal (<i>n</i> =170)	23	147		
N/A (<i>n</i> =85)	9	76		
Coexistent Hashimoto's				
No (<i>n</i> =337)	31	306	0.52 [0.26–1.07]	0.08
Yes (<i>n</i> =74)	12	62		
Use of antihypertensive medications				
No (<i>n</i> =321)	33	288	0.92 [0.43–1.94]	0.82
Yes (<i>n</i> =90)	10	80		

^aOdds ratio is for risk of nasal side effects in females compared with males, rhTSH preparation versus withdrawal preparation, those with lacrimal side effects versus those without, use of lemon candy versus no use, and so forth.

prospective investigations of the frequency of nasal and lacrimal symptoms associated with RAI, compared with an appropriate control group, along with determination of the risk factors for their development.

The mechanism of nasal damage may be different from the causative mechanism for salivary damage. Salivary glands have the ability to specifically concentrate iodine via the sodium iodide symporter (17), leading to active accumulation of radioactive material within the glands. Salivary gland damage occurs in a dose-dependent manner and reported incidence rates vary from 5% to 86% (1–3,18–21). More damage seems to occur with treatment protocols involving withdrawal from thyroid hormone than with rhTSH protocols (21). The parotid glands suffer damage more frequently than the submandibular glands (3,20,22). Salivary gland dysfunction can be manifest as sialadenitis, xerostomia, taste alterations, hypogeusia, and sialolithiasis. Dental caries, stomatitis, salivary gland or oral infections, facial nerve damage, and even salivary gland neoplasia have been described (2, 3). The reported frequency of such side effects varies widely. Although side effects such as xerostomia may be transient, they may also persist for longer periods, be delayed in onset, or even be permanent (23,24).

Similarly, lacrimal damage may be caused by specific transport of radiolabeled iodine. The ciliary body of the eye (25), the nasolacrimal duct (26), and lacrimal gland ductal cells (27) all transport iodine and seem to express the sodium

iodide symporter (27–30). Inorganic iodine within the lacrimal system may serve as an antimicrobial agent. As previously mentioned, RAI has been demonstrated within tears after oral RAI ingestion (4). The peak concentration appears to occur at about 60 minutes, with 0.01% of the administered dose being secreted with 4 hours (4). Thus, the damage caused to the lacrimal system by RAI is likely explained by active accumulation of ¹³¹I.

Nasopharyngeal tissues were found not to express the sodium iodide symporter (31), in contrast to the finding of its expression in extrathyroidal tissues such the salivary glands (31) and lacrimal system (30). Thus, it would appear likely that iodine is transported nonspecifically from the lacrimal system into the nasal ducts, and then from the interstitial surface of nasal ducts into the ductal lumen and out onto the nasal mucosal surface. However, it is also possible that there is as yet undocumented uptake by mucous cells within the nose, given that the prior studies seem to show radioactivity mostly in the tip of the nose, rather than along the course of the nasal ducts (13,14). Moreover, in the case report by McCready (13) activity was not decreased by rinsing the nose with saline.

In our index patient, her nasal complaints were not attributed to her RAI therapy by the physician to whom she reported her signs and symptoms. We cannot comment on the attribution of symptoms in our full cohort of patients, but our index patient did receive an antibiotic that was presumably unnecessary. Lacrimal symptoms, similarly, have been

documented as incorrectly diagnosed and subjected to non-specific therapies in 70% of patients (7). Bothersome nasal and lacrimal symptoms may be acceptable if these iatrogenic disorders are of less consequence than the anticipated benefits of RAI. It is important then to consider that there is no benefit of RAI in many patients with stage I disease (32,33).

Salivary side effects or measures of salivary dysfunction after RAI therapy are generally related to the dose of RAI administered (2,8,21,34–36). Similarly, nasal side effects also seemed to be directly related to the dose administered in this study. Few studies have examined the relationship between lacrimal damage and RAI dose, but one study suggested that damage occurred with higher doses (21) and another study only identified a relationship with age, but not RAI dose (11). This study did implicate higher RAI doses as being a risk factor for more lacrimal side effects. Lower rates of salivary gland and lacrimal damage seems to be sustained with protocols using rhTSH for preparation for RAI (21), a finding that was also seen for lacrimal and nasal side effects in the present study. These observations appear logical, as tissue damage would be expected to be related to the administered activity of the radioisotope and also its clearance from the body, which might be slower in the hypothyroid state, with its attendant impaired renal function. An association between higher BMI and less salivary and lacrimal damage has not been previously reported. However, such an association would appear consistent with the amount of whole body exposure perhaps being mitigated by a larger BMI. It is possible that RAI clearance is also affected by body composition. The failure of nasal symptoms to be related to lacrimal symptoms in multivariate analysis is probably explained by the fact that the association between these side effects is, in fact, due to the highly influential factors of RAI dose and method of preparation.

It appears that the nasal side effects of RAI declared themselves within 1–2 weeks of the therapeutic dose. They then appeared to resolve. It may be that these temporary side effects represent the full extent of any nasal manifestations of RAI and that there is no impairment of nasal dysfunction. However, this study was not designed to detect longer-term evidence of damage to the nasal mucosa that may be subtler in its manifestations. For example, it cannot be determined whether any individuals within this cohort suffered from chronic decrements in their sense of smell, experienced nasal sensitivity, dryness, or noted other nasal dysfunction that was not sufficiently bothersome for them to report to a physician, or for their physician to document in their medical record. The study methodology also does not permit comments on the possibility of alterations in the immunologic and antimicrobial environment of the nasal mucosa. Presumably such chronic effects are unlikely unless high-dose or repeated RAI therapy is employed, because of the regenerative capacity of the nasal mucosa (37). However, it would be important to determine if there are any long-term consequences of nasal damage, as, only if there are, would this be important for the purposes of deciding whether or not to administer RAI therapy.

Even if there are no long-term consequences of these nasal manifestations, the imaging of the nasal area nevertheless illustrates one of the routes that RAI takes as it is eliminated from the body. In addition to RAI uptake within the area of the nose itself (13,14,38), uptake due to RAI contamination of nasal secretions had been described in a nose ring (39) and

handkerchiefs retained in pockets (40,41). In this sense, nasal uptake could be likened to many of the other causes of iodine uptake visualized on whole body scanning that does not indicate residual or recurrent thyroid cancer. Such uptake includes RAI accumulation in sweat, the urinary tract, lactating breast, and swallowed saliva (42).

This study has multiple limitations. Firstly, this study only suggests an association between RAI and the described nasal side effects. Assuming that there is indeed an association, given that this is a retrospective study, it cannot truly estimate the incidence of nasal side effects, which could be calculated from a prospective study, which incorporates close monitoring and appropriate questionnaires. It is recognized that use of ICD-9 codes and the selected signs and symptoms could well either overestimate or underestimate the frequency of nasal side effects, so that the frequency of symptoms reported in this study is an imprecise estimate. Some of our patients' symptoms could have been caused by other factors such as viral infections, bacterial infections, allergies, or air conditioning, to mention but a few possibilities. In addition, since patients were not routinely monitored weekly after receiving RAI therapy, the exact onset of nasal symptoms could be inaccurate. Not all patients presented with nasal symptoms, but some presented for other reasons and subsequently described or recalled their symptoms. Moreover, this study is simply describing symptoms, but unfortunately is not providing information about nasal function *per se*, or its impairment.

This analysis also cannot demonstrate that there is cause and effect. However, this does not mean that it is not important for physicians to be aware of these side effects that appear to be temporally related to RAI. Although only few specific reports of nasal uptake or complaints could be identified in the scientific literature (13–15,38), while preparing this discussion it was discovered that the websites of thyroid cancer support groups are replete with numerous reports of nasal pain, nasal dryness, and nose bleeds in the 1–2 weeks period after RAI administration. Patients describe their frustration about not having been warned of such side effects, their experience with physicians advising them that these symptoms are unrelated to RAI, and their use of remedies such as nasal application of petroleum gel (vaseline), other gels, nasal sprays, and cotton swabs.

In summary, nasal side effects appear to occur at a rate of approximately 10%: a rate that is similar to the rate of occurrence of lacrimal dysfunction in this study. Although it cannot be determined whether these apparently temporary nasal side effects had any long-term or permanent ramifications, the exposure of nasal tissue to RAI is a reminder that nonthyroid tissue can be affected by RAI, and that the benefits and risks of RAI therapy for patients thyroid cancer should be carefully evaluated on an individual basis. This is particularly important given that thyroid cancer continues to be diagnosed with increasing frequency (43).

Acknowledgments

This project was funded in part with Federal funds (UL1TR000101 previously UL1RR031975) from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through the Clinical and Translational Science Awards Program (CTSA), a trademark of

DHHS, part of the Roadmap Initiative, “Re-Engineering the Clinical Research Enterprise.”

Author Disclosure Statement

The author has no relevant disclosures.

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