

## COMMENT

# Nasolacrimal Drainage System Obstruction from Radioactive Iodine Therapy for Thyroid Carcinoma

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Ophthalmic complications of  $^{131}\text{I}$  therapy, including ocular dryness, have been recently investigated and described. However, nasolacrimal drainage system obstruction (NDSO), complicating  $^{131}\text{I}$  therapy, has not been previously well appreciated or characterized. One of our patients developed bilateral complete nasolacrimal duct obstruction after  $^{131}\text{I}$  therapy that prompted awareness of this potential complication. Over 16 months, 423 patients with epithelial-derived thyroid cancer were provided routine clinical care; 390 of these patients had received  $^{131}\text{I}$  ablation or therapy, and 10 patients subse-

quently reported epiphora. All had evidence of NDSO disease after a mean cumulative  $^{131}\text{I}$  dose of  $17,279 \pm 2,923$  MBq ( $467 \pm 79$  mCi), with a mean individual  $^{131}\text{I}$  dose of  $6,660 \pm 555$  MBq ( $180 \pm 15$  mCi). Symptoms appeared  $6.5 \pm 1.4$  (range, 3–16) months after the last  $^{131}\text{I}$  dose, whereas the mean time from symptom onset to correct diagnosis was  $18 \pm 5$  months. A causal relationship between  $^{131}\text{I}$  administration and NDSO is strongly suspected. Patients reporting epiphora should be evaluated promptly by an oculoplastic surgeon. (*J Clin Endocrinol Metab* 87: 5817–5820, 2002)

RADIOACTIVE IODINE HAS been used in the therapy of differentiated thyroid cancer since 1946 (1–3). Common complications from this therapy are relatively minor, and severe complications are uncommon (4, 5). Recently, one of our patients reported symptoms of epiphora starting 4 months after a dose of 16,650 MBq (450 mCi) of  $^{131}\text{I}$  to treat scan-negative, thyroglobulin-positive pulmonary metastases from tall cell variant papillary thyroid cancer (PTC) and was found to have bilateral nasolacrimal duct (NLD) obstruction requiring dacryocystorhinostomy (DCR). This case raised questions about the correlation between radioactive iodine therapy and nasolacrimal drainage system obstruction (NDSO), its frequency, patterns of presentation, and optimal prevention or therapy.

### Subjects and Methods

Since May 23, 2000, we have been more aware of the possibility of NLD drainage system complications from radioiodine therapy. Between May 23, 2000 and September 23, 2001, a total of 423 patients with epithelial-derived thyroid cancer (differentiated and anaplastic thyroid cancers) have been seen in The Ohio State University outpatient thyroid clinic of one endocrinologist (R.T.K.) for clinical care. Those patients who spontaneously reported epiphora (watery eye, an overflow of tears onto the lid caused by narrowing of the tear-drainage apparatus) or who reported epiphora, after brief questioning, were referred for ophthalmological consultation. However, no systematic attempt at screening or questioning of patients was performed.

Abbreviations: DCR, Dacryocystorhinostomy;  $\text{Na}^+/\text{I}^-$ , sodium/iodide; NDSO, nasolacrimal drainage system obstruction; NLD, nasolacrimal duct; PTC, papillary thyroid cancer.

### Statistics

All results are reported as mean  $\pm$  SE. Percentages are rounded to the nearest integer.

### Results

A total of 218 of the 423-patient cohort (52%) have demonstrated extrathyroidal [ $\text{pT}_4(6)$ ] extension of disease (71 patients); incomplete primary tumor resection (32 patients); or cervical (161 patients), lung (56 patients), bone (13 patients), mediastinal (18 patients), or other metastases (14 patients) during the course of their disease. A total of 390 of the cohort (92%) have received  $^{131}\text{I}$  ablation or therapy.

Ten patients were identified with epiphora (Tables 1 and 2). The age at the onset of symptoms was  $48 \pm 6$  yr (range, 13–74). All had evidence of NDSO, and all had previously received  $^{131}\text{I}$  treatment, for an incidence of 3% among those 390 patients who have received  $^{131}\text{I}$ . The mean cumulative  $^{131}\text{I}$  dose was  $17,279 \pm 2,923$  MBq ( $467 \pm 79$  mCi), with a median cumulative dose of 16,021 MBq (433 mCi). The mean individual  $^{131}\text{I}$  dose was  $6,660 \pm 555$  MBq ( $180 \pm 15$  mCi). Symptoms appeared  $6.5 \pm 1.4$  (range, 3–16) months after the last  $^{131}\text{I}$  dose. The time from symptom onset to correct diagnosis was  $18 \pm 5$  months. Before definitive ophthalmologic diagnosis, 70% of the patients were given at least one medication or instruction (range, 0–6) by a physician to treat eye signs or symptoms consistent with the diagnosis of lacrimal drainage system obstruction (Table 3), or for a condition with signs and symptoms that may mimic lacrimal drainage system obstruction (Table 4). Therapies included warm compresses, ophthalmic antibiotics, ophthalmic glucocorticoids, artificial tears and ointment, nasal glucocorticoids, eye drops

**TABLE 1.** Details of patients, tumor (T)-node(N)-metastasis (M) stage, <sup>131</sup>I therapies (Rx), and onset of ophthalmologic symptoms

Patient no., age at symptom onset, sex	Tumor type and worst stage (6) at <sup>131</sup> I Rx	Total <sup>131</sup> I Rx before symptoms in MBq (mCi)	<sup>131</sup> I doses in MBq (mCi)	<sup>131</sup> I dates	Months from last <sup>131</sup> I Rx to symptoms
No. 1, 41 yr, Female	PTC T <sub>3</sub> N <sub>0</sub> M <sub>0</sub>	5550 (150)	5550 (150)	8/99	5
No. 2, 58 yr, Female	Follicular thyroid cancer T <sub>2</sub> N <sub>0</sub> M <sub>1</sub>	7400 (200)	7400 (200)	3/97	3
No. 3, 45 yr, Female	PTC T <sub>2</sub> N <sub>1</sub> M <sub>0</sub>	9546 (258)	3996 (108) 5550 (150)	1/99 2/00	9
No. 4, 40 yr, Female	PTC	12247 (331)	5550 (150)	8/99	3 (lasted 2 months after 1st <sup>131</sup> I), 3 (permanent after 2nd Rx)
No. 5, 41 yr, Female	T <sub>4</sub> N <sub>1</sub> M <sub>0</sub> PTC T <sub>2</sub> N <sub>1</sub> M <sub>1</sub>	12950 (350)	6697 (181) 5550 (150) 3700 (100) 3700 (100)	3/00 9/93 9/94 9/99	6
No. 6, 66 yr, Male	PTC T <sub>2</sub> N <sub>1</sub> M <sub>1</sub>	19092 (516)	5698 (154) 5994 (162) 7400 (200) XRT <sup>a</sup>	8/97 4/98 12/98 8/99	12
No. 7, 61 yr, Male	PTC tall cell variant T <sub>2</sub> N <sub>1</sub> M <sub>1</sub>	22311 (603)	5661 (153) 16650 (450)	6/97 9/99	4
No. 8, 74 yr, Male	PTC T <sub>4</sub> N <sub>1</sub> M <sub>0</sub>	24050 (650)	3700 (100) 7400 (200) 5550 (150) XRT <sup>a</sup>	10/93 5/94 6/97 10/98	16
No. 9, 13 yr, Female	PTC T <sub>4</sub> N <sub>1</sub> M <sub>1</sub>	25160 (680)	7400 (200) 2960 (80) 11100 (300) 11100 (300)	6/99 8/96 2/97 8/97	3
No. 10, 39 yr, Female	PTC T <sub>3</sub> N <sub>1</sub> M <sub>1</sub>	34595 (935)	6438 (174) 6401 (173) 6475 (175) 7881 (213) 7400 (200)	6/87 6/88 4/91 2/98 12/98	4

<sup>a</sup> 56 Gy external beam radiation therapy (XRT) to neck.

for allergies, Opcon-A, oral decongestant, Allfen, and bilateral punctal plugs.

All patients with NDSO who underwent ophthalmic intervention directed specifically at their obstructive disease (*e.g.* balloon dilation, stent, DCR, conjunctival DCR) stated that they would undergo the procedure again. Of the 10 individual lacrimal systems that had a procedure, 8 experienced complete (4 systems) or partial (4 systems) symptom relief. One patient (no. 5) underwent bilateral balloon dilatation and SILASTIC tube intubation for bilateral partial NLD stenosis, without relief, and is now considering bilateral DCR.

### Discussion

Solans *et al.* (7) prospectively investigated the prevalence of ocular and oral dryness (sicca syndrome) after <sup>131</sup>I therapy [925–18,500 MBq (25–500 mCi)]. Objective xerostomia or xerophthalmia was present in 51% and 18%, respectively, during the first year. Totals of 73% of xerostomia and 57% of xerophthalmia resolved in the third year of follow-up; however, new cases developed, such that, in the third year, 49% of the cohort had objective xerostomia and 10% had objective xerophthalmia. All patients with reduced lacrimal gland function also showed reduced salivary gland function. A correlation between cumulative <sup>131</sup>I activity and salivary

gland dysfunction and subjective xerophthalmia was found but not with objective xerophthalmia.

Alexander *et al.* (4) investigated intermediate and long-term side effects (occurring less or more than 3 months after therapy, respectively) of thyroid cancer therapy of at least 3700 MBq (100 mCi) of <sup>131</sup>I, by interviewing 203 patients. More than 1 yr after the last therapy, they found that 43% suffered from reduced salivary gland function, and 23% reported chronic or recurrent conjunctivitis. As opposed to conjunctivitis, the occurrence of sialadenitis, dry mouth, and complete xerostomia were found to be dose dependent. At cumulative <sup>131</sup>I doses of less than 4995 MBq (135 mCi), the incidence of sialadenitis, dry mouth, and xerostomia were approximately 7%, 22%, and 3%, respectively. Peak incidences occurred at more than 9990 MBq (270 mCi), with sialadenitis, dry mouth, and xerostomia in approximately 45% or more, 40% or more, and 8%, respectively. Most pertinent to our report, Alexander *et al.* reported that 2% of their series underwent DCR. No further details were provided about these cases.

Most of our patients with lacrimal drainage system obstruction demonstrated a more advanced state of thyroid cancer [8 of 10 patients had tumor, node, metastasis (6) pT<sub>4</sub> and/or M<sub>1</sub> disease] and had received more <sup>131</sup>I therapy for persistent disease than is typically seen with differentiated

**TABLE 2.** Details of patients' ophthalmologic symptoms, diagnoses, and therapies

Patient no., age at symptom onset, sex	Initial symptoms	Months from symptoms to correct Dx	Final eye Dx	Specific eye Rx	Condition since last eye Rx
No. 1, 41 yr, Female	Epiphora bilateral	10	Left complete NLD obstruction and partial CS, right partial NLD stenosis	BD and STI right once, left twice	2
No. 2, 58 yr, Female	Epiphora left, [epiphora right 4/99 after total 37000 MBq (1000 mCi)]	48	Bilateral mild CS, bilateral complete NLD obstruction	Observation	Right epiphora resolved, left improved
No. 3, 45 yr, Female	Epiphora left	8	Left complete CP obstruction and inferior CS	Observation	1
No. 4, 40 yr, Female	Epiphora right	9	Right complete NLD obstruction	BD and STI	2
No. 5, 41 yr, Female	Epiphora right, [epiphora left 10/01 3 months after an additional 11100 MBq (300 mCi)]	15	Bilateral partial NLD stenosis	Bilateral BD and STI (now considering bilateral DCR)	1
No. 6, 66 yr, Male	Epiphora bilateral	12	Right partial NLD stenosis <sup>a</sup> and left complete NLD obstruction	Observation	1
No. 7, 61 yr, Male	Epiphora bilateral	1	Bilateral complete NLD obstruction	Right DCR twice, left DCR once, then bilateral CDCR with Jones tubes	right 2, left 4
No. 8, 74 yr, Male	Epiphora bilateral	10	Bilateral complete NLD obstruction	Bilateral DCR	4
No. 9, 13 yr, Female	Epiphora bilateral, discharge on eyelids	48	Bilateral complete NLD obstruction	Right DCR, plan left DCR	right 4
No. 10, 39 yr, Female	Epiphora right	14	Right CS, right complete NLD obstruction	Observation	1

Condition since treatment: no change (1); partial, patient would do therapy again (2); partial, patient would not do therapy again (3); complete, patient would do therapy again (4); complete, patient would not do therapy again (5). CS, Canalicular stenosis; BD, balloon dilatation; STI, SILASTIC tube intubation of the nasolacrimal drainage system; CP, common puncta; CDCR, conjunctivodacryocystorhinostomy.

<sup>a</sup> Spontaneous resolution after 6 months.

**TABLE 3.** Signs and symptoms of lacrimal drainage system obstruction

Epiphora
Discharge on eyelids
Recurring conjunctivitis
Dacryocystitis
Mass below the medial canthal tendon

thyroid carcinoma (5). This is consistent with their older age of 48 yr at the time of lacrimal drainage system obstruction, compared with the younger age of 40 yr for a subset of our patients when they were deemed clinically free of disease and studied with recombinant human TSH (8). Their more advanced disease also explains the higher median cumulative <sup>131</sup>I dose of 16,021 MBq (433 mCi) at the time of ophthalmologic symptoms, compared with the median cumulative dose of 3,885 MBq (105 mCi) given to the subset of our patients who were subsequently deemed clinically free of disease (8). These findings suggest an association of <sup>131</sup>I activity to NDSO. Because of the lack of systematic screening for epiphora, selection bias cannot be excluded as another explanation for this association, although we do not suspect it is a prominent factor. Though most patients with thyroid cancer will not require large cumulative doses of <sup>131</sup>I therapy, it should be noted that two of our patients experienced symptomatic obstruction after being treated with 7400 MBq (200 mCi) of <sup>131</sup>I or less. No patient untreated with <sup>131</sup>I therapy or

**TABLE 4.** Conditions with signs and symptoms similar to lacrimal drainage system obstruction

Allergy
Viral conjunctivitis
Keratoconjunctivitis sicca
Trichiasis or distichiasis
Eyelid malposition
Canaliculitis
Iritis
Foreign body
Increased reflex lacrimation resulting from decreased basal lacrimal secretions

treated with less than 5550 MBq (150 mCi) of <sup>131</sup>I experienced clinically apparent NDSO. The incidence of NDSO in the general population is unknown despite a detailed search of the medical literature and inquiry among members of the American Society of Ophthalmic Plastic and Reconstructive Surgery via their Internet ([www.asoprs.org](http://www.asoprs.org)) chat-line. Lacking this data, our clinical impression is that the 3% incidence of NDSO among our cohort greatly exceeds the expected incidence in the general population. The circumstantial evidence of an increased incidence of NDSO with higher activities of <sup>131</sup>I, the close temporal relationship between therapy and symptom onset, the fact that the NDSO was frequently bilateral, and the perceived increased incidence of NDSO in thyroid cancer patients treated with <sup>131</sup>I, compared with the general population, leads to our speculation of a

causal relationship. Further, 1 or more experienced ophthalmologists with specific expertise in the NLD system examined each of the 10 patients and found no other explanation for their NDSO. Thus, it is probably prudent to inform patients of this uncommon potential side effect of  $^{131}\text{I}$  therapy when administering cumulative doses of 5550 MBq (150 mCi) or more. However, because a comprehensive search for epiphora was not performed on the entire cohort of patients, the actual incidence of NDSO may be higher than reported here (indeed, we suspect that it is), and occurrence of this complication when a dose less than 5550 MBq (150 mCi) of  $^{131}\text{I}$  was administered cannot be completely excluded.

There was a delay of almost 12 months between the onset of symptoms and the correction diagnosis of NDSO. The delay in correct diagnosis may be partially explained by the decreased tear production frequently associated with  $^{131}\text{I}$  therapy or simply the lack of familiarity with the diagnosis. Management of patients with complete obstructions requires more extensive surgical procedures than does the management of patients with an incomplete obstruction. It is probable that complete obstruction is not present at the time of initial symptoms, leading to the hypothesis that early intervention with balloon dilation of the NLD (Lacricath) and/or stents may prevent complete obstruction until radiation-induced inflammatory changes subside. However, the natural history of patients presenting with partial obstruction is unknown, and data from several of our patients suggests spontaneous improvement without specific intervention.

The sodium/iodide ( $\text{Na}^+/\text{I}^-$ ) symporter is a membrane glycoprotein that mediates active iodide uptake in the thyroid gland and in several extrathyroidal tissues, including the ciliary body of the eye (9), NLD (10), and lacrimal gland ductal cells (11–13). Independent stimulation of thyroidal  $^{131}\text{I}$  uptake with simultaneous blockage of  $^{131}\text{I}$  uptake in extrathyroidal tissues is not currently possible. A possible role for the  $\text{Na}^+/\text{I}^-$  symporter-mediated secretion of inorganic iodide by the lacrimal system is to serve as an antimicrobial agent (13, 14). Leder (10) demonstrated  $^{131}\text{I}$  uptake in the NLD of rats, 5 min after iv injection, with less accumulation in the lacrimal glands. Human tears (originating largely from the lacrimal glands) have been demonstrated to contain radioactive iodine, starting 15 min after the oral ingestion of I-123, with a peak concentration at around 60 min, and a total secretion of about 0.01% of the administered dose within the first 4 h (15). The turnover rate of the tear film in the lacrimal system is approximately 12–16%/min (15). These findings lead us to postulate that the direct uptake of  $^{131}\text{I}$  in the nasolacrimal system plays a greater role in the radiation-induced injury than does the radiation exposure to the system from the simple passage of radioactive tears.

### Conclusion

We report 10 cases of lacrimal drainage system obstruction after  $^{131}\text{I}$  therapy, which represents 3% of our  $^{131}\text{I}$ -treated

thyroid cancer patients. The lowest cumulative dose of  $^{131}\text{I}$  associated with obstruction was 5,550 MBq (150 mCi), whereas the mean cumulative dose was 17,279 MBq (467 mCi). Symptoms of epiphora developed 6.5 months after the last  $^{131}\text{I}$  therapy, with incorrect diagnoses and nonspecific therapy being prescribed in 70% of patients. Definitive diagnosis was not established until an average of 18 months after therapy, with definitive intervention providing partial or complete symptom relief in most patients. Patients receiving cumulative doses of at least 5,550 MBq (150 mCi) of  $^{131}\text{I}$  should be informed of this infrequent potential complication, and physicians should be aware of its presentation, to facilitate early referral to an appropriate oculoplastic surgeon. However, before definitive conclusions can be drawn, a systematic study of this topic, with an appropriate control population and study design, will be necessary.

### Acknowledgments

Received February 2, 2002. Accepted August 27, 2002.

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