Synovial sarcoma of the lung in a patient who received radioactive iodine therapy for thyroid

cancer

Avni Vora, M.D. and Arthur B. Schneider. M.D., PhD.

Section of Endocrinology, Diabetes and Metabolism, College of Medicine, University of Illinois at Chicago, Chicago, IL 60612

Keywords: radioactive iodine, thyroid cancer, synovial sarcoma, radiation-associated malignancies

Corresponding author: Arthur B Schneider, M.D., Ph.D. University of Illinois at Chicago 1819 W Polk Street (MC 640) Chicago, IL 60612 abschnei@uic.edu

Abstract

Background: Synovial sarcomas are uncommon malignancies that mainly affect adolescents and young adults. Most arise from the deep soft tissues of the extremities, but they can occur in other parts of the body such as the lung. Synovial sarcomas after radiation therapy are rare, in contrast with other sarcomas, with only 6 reported cases. Secondary malignancies after radioactive iodine (RAI) therapy are also uncommon, with the most consistent evidence for hematologic malignancies.

Patient findings: We present what we believe to be the first report of a synovial sarcoma of the lung with an SS18/SSX1 translocation following RAI therapy. At age 20, the patient developed papillary thyroid cancer and later had two surgically confirmed recurrences. Over the course of her care she received a total of about 220 mCi of ¹³¹I. At age 34, as part of an evaluation for another suspected recurrence she had a PET/CT scan and a pulmonary mass was detected. *Summary and Conclusion:* Although not previously reported, this case suggests that synovial sarcomas may be a secondary malignancy following RAI therapy. The latency in this case is reasonable, the dose to the lungs was small, but in the range where radiation-related malignancy may occur, and the somatic chromosomal rearrangement could be a radiation effect.

Introduction

RAI has been used for decades in the treatment of differentiated thyroid cancer and prolongs disease-free and total survival in high risk patients. Even so, the potential for secondary primary malignancies (SPM) needs to be balanced against the benefit (1). The risk was evaluated in a meta-analysis by Sawka et al. in which they included two cohorts with over 37000 thyroid cancer patients in which almost 8500 received RAI therapy (2). Their analysis found that RAI therapy increases overall risk of SPM (RR of 1.19; CI 1.04-1.36). When analyzed by cancer type, only leukemia was found to be significantly related to RAI therapy (RR of 2.5; CI 1.13-5.53). However, not all studies have found an increase RR for solid malignancies and efforts to identify specific sites of solid cancers have been largely unsuccessful due to the inconsistencies among studies (1,2).

We describe a woman who developed a rare tumor, a synovial sarcoma of the lung after receiving radioiodine therapy for a recurrent papillary thyroid cancer. Although some cases of secondary primary lung malignancies have been described (3,4), Sawka et al. did not observe a statistically significant increase in them (2).

Patient

Thyroid Synovial sarcoma of the lung in a patient who received radioactive iodine therapy for thyroid cancer (doi: 10.1089/thy.2012.0472) This article has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

The patient was 20 years old in 1997 when she was diagnosed with a papillary thyroid carcinoma. She has no children and there is no history of malignancy in her parents or two brothers. There is no history of thyroid cancer in any relative.. She confirmed with her mother that she had never had childhood therapeutic radiation exposure. She underwent a total thyroidectomy and a 1.8 cm differentiated typical papillary thyroid carcinoma in the left lobe with abundant psammoma bodies, extension into the isthmus and two positive lymph nodes adjacent to the isthmus were

Page 4 of 18

- 4 -

found. No histological findings suggesting residual or an especially aggressive cancer were reported. An ¹²³I scan demonstrated uptake in the right neck and she received 60 mCi of ¹³¹I.

At age 23 years, after ultrasonically suspicious cervical lymph nodes were positive by FNA cytology for papillary thyroid cancer with the presence of nuclear inclusions and grooves, she underwent further surgery. Multiple positive lymph nodes and invasion into adipose tissue was found. An ¹³¹I scan performed two months later demonstrated persistent uptake in the neck and she received 157.6 mCi of ¹³¹I after thyroid hormone withdrawal. Afterwards, her TSH levels were suppressed and thyroglobulin levels remained undetectable. A thyrotropin alpha stimulated ¹²³I whole body scan at age 26 demonstrated no uptake and MRI of the neck and upper mediastinum at that time was also negative for metastasis. At age 29, she was noted to have suspicious lymph nodes on ultrasound. FNA demonstrated recurrent papillary thyroid cancer and 3 of 11 lymph nodes removed at surgery were positive. Subsequent ultrasounds did not demonstrate any recurrent disease.

At age 34, a previously unseen lymph node in the left central compartment of the neck was detected by ultrasound. Her thyroglobulin remained undetectable. To evaluate the lymph node further and to look for areas of thyroid cancer, a fluorodeoxyglucose position emission spectroscopy (FDG-PET) computed tomography examination was performed (Figure 1). There was no uptake of FDG-18, but a 2.9 cm mass with smooth margins and uniform density, initially suggestive of a cyst, was noted in the upper lobe of the right lung on the computed tomography component of the procedure. The mass did not take up FDG-18 and was not present in the same area visualized on MRI done at age 26. A CT-guided core biopsy of the mass demonstrated a spindle cell neoplasm with features favoring a monophasic synovial sarcoma. A video-assisted thorascopic resection was performed. As the mass had enlarged from the time of its initial

- 4 -

Page 5 of 18

discovery and as the patient had good residual lung capacity, the right middle lobe was resected in addition to the right upper lobe. A 5.4 x 4.5 x 2.7 cm mass in the right upper lobe invading into the right middle lobe was removed, with pathology consistent with monophasic synovial sarcoma (Figure 2). Surgical margins were free of tumor although the medial margin was only 2 mm as larger resection was precluded by the presence of vital structures. Immunohistochemical staining was positive for tumor markers CD56 (neural cell adhesion molecule), BCL2 (apoptosis regulator protein), EMA (epithelial surface protein) but negative for CD117 (receptor for activation of tyrosine kinase), S100 (found in malignant peripheral nerve sheath tumors with focal keratin expression), CD34 (endothelial cell marker in solitary fibrous tumors) and TTF1 (a thyroid and lung tissue marker). Total RNA was extracted from the surgical specimen and transcribed into cDNA. Using SSX1 and SSX2 primers with an SS18 primer, the pathognomonic SS18/SSX1 fusion transcript for synovial sarcoma was demonstrated. The patients' post-operative recovery was uneventful. Due to small surgical margin medially, proton beam therapy was administered, but chemotherapy was not given. There is no evidence of tumor recurrence 10 months after surgery, but she does have persistent dyspnea on exertion. The lymph node noted on previous thyroid ultrasound is no longer present by ultrasound done 12 months after the one that precipitated the discovery of the synovial sarcoma.

Discussion

Synovial sarcoma is a soft tissue sarcoma that mainly affects the deep soft tissues of the extremities in adolescents and young adults but can occur in almost any part of the body, including the lungs (5). As reported in 2000, synovial sarcoma represented 5-10% of all soft tissue sarcomas with about 800 cases per year in the Unites States (6). There tends to be a male

- 5 -

predominance. There are 4 histological types: biphasic, monophasic fibrous, monophasic epithelial, poorly differentiated. The biphasic type consists of epithelial and spindle cell components whereas the monophasic types have uniform spindle cells and are difficult to distinguish from other spindle cell neoplasms (fibrosarcoma, hemangiopericytoma, leimyosarcoma, spindle cell carcinoma, carcinosarcoma) (7). In synovial sarcomas epithelial markers, such as epithelial membrane antigen (EMA) and cytokeratin, are often present (7), but the pathognomonic finding in about 90% of cases is the t(X;18)(p11;q11) translocation (8). This is a rearrangement of the SS18 gene (formerly known as SYT) in the 18q11 region and one of the SSX1, SSX2, or SSX4 genes in Xp11. The rearrangement produces a chimeric SS18/SSX protein in which the last 8 amino acids of the SS18 protein a replaced by the carboxy-terminal part of the SSX protein. The functionality of this protein is unclear, but it may have increased transcriptional activity (8). Surgical excision is the primary treatment modality for treatment of synovial sarcoma. Radiotherapy decreases the rate of local recurrence and adjuvant chemotherapy, most commonly a combination of doxorubicin and ifosphamide, given in a few patients has been shown to increase time to local or distal recurrence, but not necessarily improve overall survival (6). In a case review done by Spillane et al. of 150 cases of synovial sarcoma, the 5 year survival rate was 57%. For synovial sarcomas in general, poor prognostic factors included tumor size >5cm, age greater than 20 at diagnosis, and the SS18 (SYT)-SSX1 fusion gene. The 5-year progression free survival rate associated with the SS18-SSX1 gene is 42% versus 89% for the SS18-SSX2 gene (7). However, this may not apply to the very rare pulmonary synovial sarcomas (7).

A review of 60 cases of pulmonary and mediastinal synovial sarcomas demonstrated that the most common presenting symptoms are dyspnea and chest pain (5). Pulmonary and mediastinal

- 6 -

Thyroid Synovial sarcoma of the lung in a patient who received radioactive iodine therapy for thyroid cancer (doi: 10.1089/thy.2012.0472) This article has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

synovial sarcomas tend to present in older patients without sex bias. The tumors tend to be more aggressive with 40% presenting as poorly differentiated and an overall 5year survival rate of 54%. The majority of the patients (58%) had the *SS18-SSX1* translocation.

Post-radiation sarcomas have been defined as sarcomas arising in a previously irradiated field after a latency period of at least 2 years (9). Post-radiation sarcomas have been reported with latencies ranging from 3 to 55 years and typically occur following treatment doses ranging from 45 to 60 Gy. Synovial sarcoma after radiation therapy is rare, with only 6 cases reported in the literature (Table 1). In 1978, Mischler et al. described biphasic synovial sarcoma of the neck after facial and neck radiation for acne, although this case was not confirmed by immunohistochemical or cytogenetic data (10). In 1997, van de Rijn et al. described a 36 yearold woman with synovial sarcoma of the brachial plexus 8 years after receiving chemotherapy and 77 Gy for the treatment of Hodgkin's lymphoma (11). Egger et al. described two cases, the first of which was a 42 year-old woman who developed synovial sarcoma of the minor pectoral muscle 17 years after receiving 171 Gy for breast carcinoma (12). The second patient was a 34 year-old woman who developed synovial sarcoma of the left hand after receiving an unknown dose of radiation to the hand at age 7 for congenital hemihypertrophy secondary to angiomatous malformation. Dereaedt et al. reported synovial sarcoma of the left lung in a 20 year-old male with history at age 4 of a metastatic Wilm's tumor that was treated with nephrectomy, pre- and post-operative chemotherapy, and post-operative pulmonary and abdominal radiation (9). Lastly, Mullah-Ali et al. described a paraspinal synovial sarcoma in a 14 year-old girl treated with chemotherapy and 24 Gy to the abdomen and pelvis for neuroblastoma at the age of 14 months (13). The latter 5 cases of synovial sarcoma were confirmed with analyses demonstrating the

- 8 -

t(X;18)(p11.2;q11)) translocation and all had the monophasic morphology. Four out of six of these cases occurred in females and the range of latency was 8-27 years.

The exact pulmonary exposure from the RAI therapy in the patient described here is not known, as jodine kinetics were not measured, but an estimate can be made. Kolbert et al. evaluated the potential organ doses in thyroid cancer patients treated with RAI therapy (14). They evaluated 26 patients with known metastatic papillary or follicular thyroid cancer and used a combination of PET-CT, ¹²⁴I scans under thyrotropin alpha stimulation and imaging analysis software to determine the Gray per Gigabequeral (Gy/GBq) for normal organs. Blood testing demonstrated exposure of 0.1 Gy/GBq and the lung received a mean dose of 0.091 Gy/GBq. Thus, if a patient were to receive 200 mCi of ¹³¹I, a normal lung may receive about 0.7 Gy of radiation. . Our patient received RAI therapy with THW so the actual delivery of radiation dose to extra-thyroidal tissue was probably higher than 0.7 Gy. Hanscheid et al. randomized 63 patients to RAI therapy with rhTSH or THW and assessed RAI biokinetics (15). While there was no difference in 48-hour uptake and residence times in remnant thyroid tissue, rhTSH had significantly longer effective half-life in the remnant tissue and significantly lower absorbed dose to the blood. If we use the ratio observed by Hanscheid et al. for the dose delivered to the blood, we can estimate that the patient's lung received 1.1 Gy.

The patient had not been exposed to ionizing radiation to the pulmonary area other than the radioiodine therapy. If, in fact, the patient's sarcoma was related to her radioiodine therapy, why did it occur after a relatively low dose, especially in comparison to other radiation-related sarcomas? It is notable that many papillary thyroid cancers in young people carry *RET* rearrangements. For example, in 38 cases in children (5-18 years) from Belarus exposed to Chernobyl radiation and 23 sporadic cases in U.S. children more than half in each group had

- 8 -

rearrangements, although the pattern of the translocation sites differed (16). If both of the patient's cancers were the result of genetic rearrangements, perhaps she was particularly susceptible to them. It has been suggested that changes in radiation response genes may increase the risk of thyroid cancer, although the evidence remains inconclusive (17).

Conclusion

We present a patient with history of papillary thyroid cancer treated with RAI therapy who subsequently presented with synovial sarcoma of the lung. Our patient received a total of 217 mCi of ¹³¹I which is within the range reported to cause secondary primary malignancy (SPM) after RAI (3). While we cannot be sure of the amount of RAI delivery to lung (pulmonary metastases were never present on imaging), the patient developed a malignancy in the appropriate latency period when compared to other radiation-induced sarcomas. Also, the development of synovial sarcoma in the lung in proximity to thyroid gland increases suspicion for an association. In summary, considering that the patient was treated for thyroid cancer at a young age and subsequently developed a rare synovial sarcoma with a gene rearrangement, there may have been an association between her RAI treatment and the subsequent development of a synovial sarcoma.

Reference List

- 1 Schneider AB, Viana MA, Ron E 2009 Weighing shadows: can meta-analysis help define the riskbenefit ratio of RAI treatment for low-risk thyroid cancer patients? Thyroid **19**:435-436.
- 2 Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, Straus S, Ezzat S, Goldstein DP 2009 Second primary mailignancy risk after radioactive iodine treatment for thryoid cancer: A systematic review and meta-analysis. Thyroid **19**.
- 3 Lang BH, Wong IO, Wong KP, Cowling BJ, Wan KY 2012 Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. Surgery **151**:844-850.
- 4 Laing RW, Saunders MI 1992 A case of lung carcinoma induced by radioactive iodine given for disseminated thyroid carcinoma. Clin Oncol (R Coll Radiol) **4**:394-395.
- 5 Hartel PH, Fanburg-Smith JC, Frazier AA, Galvin JR, Lichy JH, Shilo K, Franks TJ 2007 Primary pulmonary and mediastinal synovial sarcoma: a clinicopathologic study of 60 cases and comparison with five prior series. Mod Pathol **20**:760-769.
- 6 Spillane AJ, A'Hern R, Judson IR, Fisher C, Thomas JM 2000 Synovial sarcoma: a clinicopathologic, staging, and prognostic assessment. J Clin Oncol **18**:3794-3803.
- 7 Hosono T, Hironaka M, Kobayashi A, Yamasawa H, Bando M, Ohno S, Sohara Y, Sugiyama Y 2005 Primary pulmonary synovial sarcoma confirmed by molecular detection of SYT-SSX1 fusion gene transcripts: a case report and review of the literature. Jpn J Clin Oncol **35**:274-279.
- 8 Storlazzi CT, Mertens F, Mandahl N, Gisselsson D, Isaksson M, Gustafson P, Domanski HA, Panagopoulos I 2003 A novel fusion gene, SS18L1/SSX1, in synovial sarcoma. Genes Chromosomes Cancer **37**:195-200.
- 9 Deraedt K, Debiec-Rychter M, Sciot R 2006 Radiation-associated synovial sarcoma of the lung following radiotherapy for pulmonary metastasis of Wilms' tumour. Histopathol **48**:473-475.
- 10 Mischler NE, Chuprevich T, Tormey DC, Ramirez G, Mack EA 1978 Synovial sarcoma of the neck associated with previous head and neck radiation therapy. Arch Otolaryngol **104**:482-483.
- 11 van de Rijn M, Barr FG, Xiong QB, Salhany KE, Fraker DL, Fisher C 1997 Radiation-associated synovial sarcoma. Hum Pathol **28**:1325-1328.
- 12 Egger JF, Coindre JM, Benhattar J, Coucke P, Guillou L 2002 Radiation-associated synovial sarcoma: clinicopathologic and molecular analysis of two cases. Mod Pathol **15**:998-1004.
- 13 Mullah-Ali A, Ramsay JA, Bourgeois JM, Hodson I, Macdonald P, Midia M, Portwine C 2008 Paraspinal synovial sarcoma as an unusual postradiation complication in pediatric abdominal neuroblastoma. J Pediatr Hematol Oncol **30**:553-557.

- 14 Kolbert KS, Pentlow KS, Pearson JR, Sheikh A, Finn RD, Humm JL, Larson SM 2007 Prediction of Absorbed Dose to Normal Organs in Thyroid Cancer Patients Treated with 131I by Use of 124I PET and 3-Dimensional Internal Dosimetry Software. J Nucl Med **48**:143-149.
- 15 Hänscheid H, Lassmann M, Luster M, Thomas SR, Pacini F, Ceccarelli C, Ladenson PW, Wahl RL, Schlumberger M, Ricard M, Driedger A, Kloos RT, Sherman SI, Haugen BR, Carriere V, Corone C, Reiners C 2006 lodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med **47**:648-654.
- 16 Nikiforov YE, Rowland JM, Bove KE, Monforte-Munoz H, Fagin JA 1997 Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. Cancer Res **57**:1690-1694.
- 17 Williams D 2009 Radiation carcinogenesis: lessons from Chernobyl. Oncogene 27 Suppl 2:S9-18.

Thyroid Synovial sarcoma of the lung in a patient who received radioactive iodine therapy for thyroid cancer (doi: 10.1089/thy.2012.0472) This article has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Figure legends

- 12 -

Page 13 of 18



Figure 1. PET-CT examination showing the right upper lobe pulmonary mass (arrow). There was moderate PET enhancement in a left axillary lymph node (SUV = 4.08), thought to be due to extravasation of FDG seen in the antecubital fossa, but no enhancement of the pulmonary mass.

Page 14 of 18

- 14 -



Figure 2. Panel A: H& E Stain (magnification 20 x); Panel B: Positive immunohistochemistry for BCL2 (magnification 40 x); Panel C: Positive immunohistochemistry for CD56 (magnification 40 x).





Figure 1 (color version)

Page 16 of 18

- 16 -



Figure 2 (color version)

Case (Ref)	Mishler et al.	Van de Rijn et	Egger et al. Case	Egger et al. Case	Deraedt et al. (9)	Mullah-Ali et al.	Current Case
	(10)	al. (11)	1 (12)	2 (12)		(13)	
Sex/Age*	M/28	F/36	F/42	F/34	M/20	F/14	F/34
Primary	Acne	Nodular	Poorly dif-	Vascular	Wilms tumor in	Left retro-	Papillary thyroid
Malignancy		Sclerosing	ferentiated	malformation	left kidney with	peritoneal stage	cancer
		Hodgkin's	carcinoma of the	with left hand	lung metastases	III neuro-	
		Lymphoma	right breast	gigantism		blastoma	
		(Stage IIa)					
Treatment	RT	RT, CT for	Mastectomy, LN	RT	CT + left	CT as per	Total
Modalities		tumor relapse 1	dissection, RT		nephrectomy,	[#] MADDOC	thyroidectomy +
		year later			post-operative	protocol, RT	LN dissection +
					RT		RAI therapy
Irradiation	Face and neck (4	33 Gy to	50 Gy to right	RT of hand,	RT of lungs and	RT to left	60 mCi of RAI,
Modalities	courses),	periaortic region	breast (21 Gy to	dose NA	abdomen,	abdomen and	then 157.6 mCi
	dose NA	and splenic	tumor), 52 Gy to		dose NA	pelvis; 2.4 Gy in	for recurrence
		pedicle; 44 Gy to	supraclavicular			16 fractions	
		mantle field	and axillary LNs,				
			48 Gy to para-				
			sternal LN				
Latency (yr)	14	8	17	27	16	13	14
Site and size of	Neck near right	Left infra-	Right sub-	Left hand, 2cm	Two lesions in	Left lumbar	Right upper and
SS	thyroid lobe,	clavicular	clavicular		left upper lobe of	paraspinal	middle lobe of
	3.5 cm	region, 3cm	region, 5.5 cm		lung, size NA	region, 7.5 x 6.0	lung, 5.4 x 4.5 x
						x 2.0 cm,	2.7 cm
Histol-	Biphasic/NA	Monophasic/G2	Monophasic/G2	Monophasic/G3	Monophasic/NA	Monophasic/G2	Monophasic/G2
ogy/Grade**							
Translocation	NA	SS18–SSX2	SS18-SSX1	SS18 -SSX1	Present, type	Present, type	SS18-SSX1
					unknown	could not be	
						distinguished	
Treatment	Wide excision +	Incisional biopsy	Wide excision	Local excision +	NA	Debulking	Local excision +
	right LN dis-	only; wide ex-		amputation of		excision + RT +	RT
	section	cision impossible		third digit + RT		CT	
				+CT			

Table 1: Clinicopathological Features of Post-Radiation Synovial Sarcoma

Page 18 of 18

Follow-up	Local recurrence	NA	Local recurrence	Lung metastases	NA	On treatment,	Alive without
	at 10 months		at 18 months,	at 12 months,		clinically stable	disease at 10
			alive without	alive with		with possible	months
			disease at 23	disease		pulmonary	
			months			metastases	

*Age at time of diagnosis of synovial sarcoma

**Grade according to French Federation of Cancer Centers (FNCLCC) grading system

[#]MADDOC protocol: nitrogen mustard, doxorubicin, dacarbazine, cisplatin, vincristine, cyclophosphamide

CT indicated chemotherapy, M, male; F, Female; mets, metastasis; NA, not available;

RT, radiotherapy; SS, synovial sarcoma; RAI, radioactive iodine therapy