J of Nuclear Medicine Technology, first published online October 5, 2020 as doi:10.2967/jnmt.120.249128

Title: Axillary lymph nodal metastases from thyroid carcinoma: report of two cases with review of literature

Abbreviated Title: ALNM in thyroid carcinoma

Shashank Shekhar Singh[1], MD rahul.sin880@gmail.com

Swathy Krishnan[1], MBBS swathykrishnan0715@gmail.com

Nitheeshraj K Tigapuram[1], MBBS kamalnitheesh912@gmail.com

Ashwani Sood[1*], DNB sood99@yahoo.com

Swayamjeet Satapathy[1], MBBS swayamjeet.satapathy@gmail.com

Manish Rohilla[2], MD rohillamanishpgi@gmail.com

Sindhu Tanigassalam[1], MBBS paramusindhu@gmail.com

Bhagwant Rai Mittal[1], DNB, MD brmittal@yahoo.com

Affiliation:

[1]Department of Nuclear Medicine and [2]Department of Cytopathology and Gynecological Pathology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh-160012, India

Corresponding Author

Dr Ashwani Sood, DNB

Additional Professor

Department of Nuclear Medicine,

PGIMER, Chandigarh-160012, INDIA

Phone: 91-172-2756728; Fax: 91-172-2742858

Email: sood99@yahoo.com

First Author:

Shashank Shekhar Singh, Resident

Department of Nuclear Medicine

Postgraduate Institute of Medical Education and Research

Chandigarh, India- 160012

Tel: +91-7760700564

Fax: +91-172 2742858

Email: rahul.sin880@gmail.com

Word Counts of the manuscript: 750

Financial support for the work: There is no financial disclosure

Conflict of interest: None

Abstract:

Thyroid carcinoma has excellent long-term outcome for loco-regional disease with adequate treatment, however outcome declines sharply in distant metastatic disease. Axillary lymph nodal metastases (ALNM) are very unusual in thyroid carcinoma with poorer outcome as they are usually associated with aggressive histopathologies, extensive loco-regional and distant metastatic disease. The authors report two patients of thyroid carcinoma with ALNM and their management, and review of literature of such cases.

Keywords: Thyroid carcinoma; axillary lymph node; metastases; radioiodine

Thyroid carcinomas are indolent in nature with excellent long-term prognosis in early stages, however declines sharply with distant metastases. Thyroid carcinomas typically metastasize to lungs, bones, liver and brain apart from neck lymph nodes *(1)*, but rarely involve axillary lymph nodes (ALN). Here we report two patients of histological variant differentiated thyroid carcinoma having ALN metastases (ALNM) with review of literature.

Case1: A 69-year-old woman with papillary thyroid carcinoma (PTC) on cytopathology from right-sided neck swelling of 5 years duration underwent total thyroidectomy, central neck dissection and right IJV ligation. Histopathology revealed multicentric columnar cell variant of PTC with 14/19 lymph nodal metastases. Her stimulated serum thyroglobulin (Tg:1409 ng/mL) was elevated with normal anti-thyroglobulin antibody (ATg:30 IU/mL). Diagnostic iodine-131 whole-body scan (DxWBS) and SPECT/CT, followed by FDG PET/CT showed non-iodine avid but intensely FDG avid bilateral cervical nodes, right ALN and a right lung nodule (~2.0x2.0 cm) (Fig 1). Ultrasound-guided cytopathology of right ALN was suggestive of metastatic PTC (Fig 2).

Post-therapy whole-body scan (PTWBS) following empirical iodine-131 (~150 mCi) showed faint tracer uptake in the right supraclavicular region. Thalidomide and suppressive dose of levothyroxine was started in view of negative iodine scan and elevated Tg. Six months later, she showed substantial decline in serum Tg (13.7 ng/mL) and ATg (<15 IU/mL) and is presently asymptomatic on follow-up.

Case2: A 70-year-old woman with PTC on cytopathology for midline neck swelling for 2 months underwent total thyroidectomy and left selective neck dissection. Histopathology revealed tall-cell variant PTC with capsular invasion, single intra-thyroidal and 3 cervical metastatic nodes (4/20).

In view of her stimulated Tg (187 ng/mL) and ATg (19.5 IU/mL) values, intermediate risk-category and tracer avid remnant on DxWBS, iodine-131 (~100 mCi) was administered. PTWBS and SPECT/CT localized tracer avid remnant, few highest mediastinal, prevascular nodes and single left ALN. Post 6-months, DxWBS showed no tracer uptake in thyroid bed and left axilla with few foci of mediastinal tracer uptake, and stimulated serum Tg (102 ng/mL) and ATg (<15 IU/mL) respectively (Fig 3). Suppressive dose of levothyroxine was started because of her old age and poor general condition. She succumbed to respiratory failure after 19 months of initial diagnosis.

Discussion:

A total of 31 including two present cases of histopathologically proven thyroid carcinoma with ALNM are reviewed (supplementary table 1 with references). IEC approved this retrospective study and requirement to obtain informed consent was waived, INT/IEC/2020/SPL-921.

Both genders were almost equally affected (16 men, 15 women) with mean age of 51.6 years (range: 19-69). Twenty-one patients had primary tumor histology of PTC and eight of them had high-risk variants/poorly-differentiated component. Other histopathologies were medullary thyroid carcinoma (n=5) and follicular thyroid carcinoma (n=2), with mucoepidermoid carcinoma, mucin-producing adenocarcinoma, and sclerosing muco-epidermoid carcinoma (rare histopathologies) in each patients.

Twenty-four and one out of 31 patients had N1b and N1a disease at presentation. Nodal status was unknown in 5 patients whereas one patient had no nodal involvement. Of 31 patients, 11 had ALNM at initial presentation (concurrent disease) and 19 had late presentation (recurrent disease) with mean duration of 14.3 years (range: 3 months-41 years) from the initial management, while status of one patient was unknown in the study cohort.

Fourteen of 31 patients had metastatic disease at initial presentation, four of them showed ALNM only as single metastatic site, whereas 10 had additional metastatic lesions in lung (n=8), skeletal (n=3), liver (n=2) and pericardial effusion (n=1).

Most patients with histological variant/poorly-differentiated thyroid carcinoma had ALNM at presentation or within few months of presentation of the primary disease. Though, majority of patients with PTC had ALNM as recurrent disease in the follow-up. Two of the patients with initial PTC turned nearly 10 years later into PTC with aggressive variants in recurrent axillary lymph node(s) on histopathology, suggesting that well-differentiated PTC could have transformed into poorly-differentiated carcinoma during the disease course *(2,3)*.

Postulated mechanisms for thyroid carcinoma metastasizing to ALN may be direct communication between cervical and axillary lymphatics, retrograde dissemination to regional lymphatic channels or hematogenous dissemination *(4,5)*. Extensive cervical nodal metastases and/or previous neck dissection may favour altered lymphatic flow secondary to lymphatic blockage or fibrosis from prior surgery.

ALNM are detected on iodine-131 scan or ^{18}F-FDG PET/CT apart from conventional imaging. Radioiodine uptake in ALN is usually synonymous with metastatic disease from differentiated thyroid carcinoma. Review of literature showed that majority were managed with ALN dissection though few were treated with iodine-131 for iodine avid disease with improved outcomes. Long-term follow-up is essential of these patients with unusual metastases involving ALN.

References:

1. Byar DP, Green SB, Dor P et al. A prognostic index for thyroid carcinoma. A study of the EORTC Thyroid Cancer Cooperative Group. *Eur J Cancer*. 1979;8:1033-41.
2. Ozaki O, Ito K, Mimura T, et al. Anaplastic transformation of papillary thyroid carcinoma in recurrent disease in regional lymph nodes: a histologic and immunohistochemical study. *J Surg Oncol*. 1999;70:45-48.
3. Sakamoto A, Kasai N, Sugano H. Poorly differentiated carcinoma of the thyroid: a clinicopathological entity for a high-risk group of papillary and follicular carcinoma. *Cancer*. 1983;52:1849-1855.
4. Kowalski LP. Non cervical lymph node metastasis from head and neck cancer. *Otorhinolaryngol Relat Spec*. 2001;63:252-255.
5. Sherman SI. Thyroid carcinoma. *Lancet.* 2003;361:501-511.

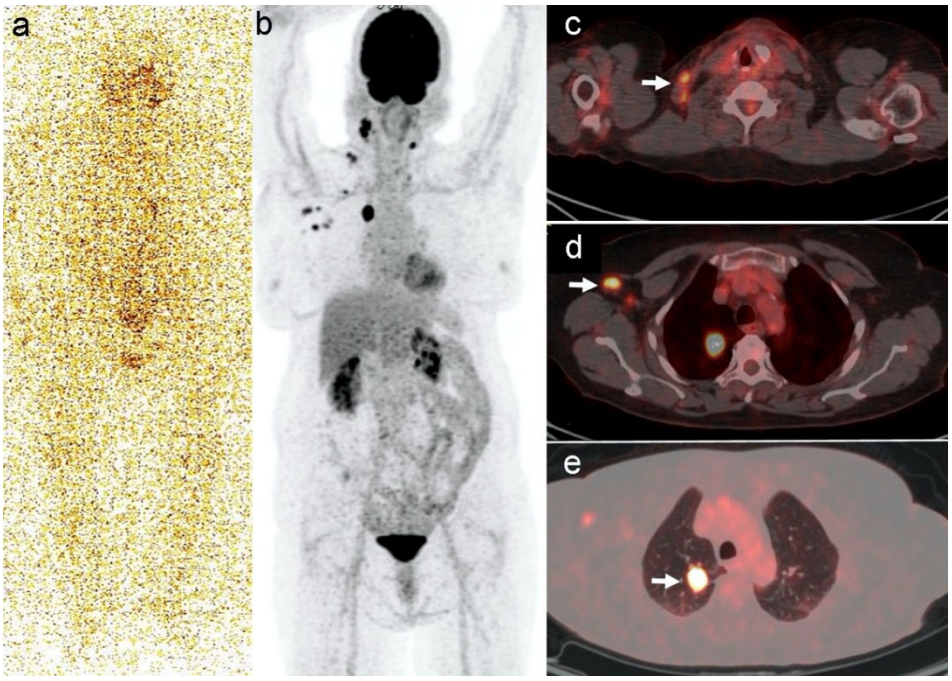

FIGURE 1 Negative diagnostic whole-body ^{131}I planar anterior image (a), ^{18}F-FDG PET/CT Maximum Intensity Projection (MIP) image (b) and fused axial images showing tracer avid bilateral cervical, right supraclavicular and right axillary lymph nodes, and right lung nodule (c-e; arrows)

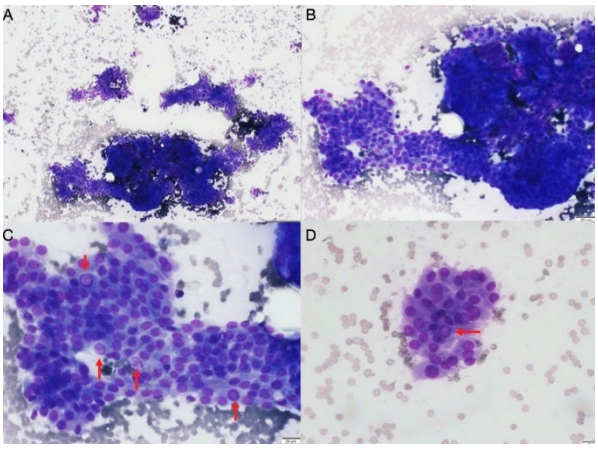

FIGURE 2 Fine needle aspiration from the right axillary lymph node yielded colloid mixed material and cellular smears. Tumor cells seen to be arranged in papillae, and small clusters (a; MGG stain; 40X); a tumor papilla with rolled-up margins (b; MGG stain; 100X). Individual tumor cells show nuclear enlargement with focal crowding and prominent intranuclear pseudo inclusion (c,d; red arrows; MGG stain; 200X)

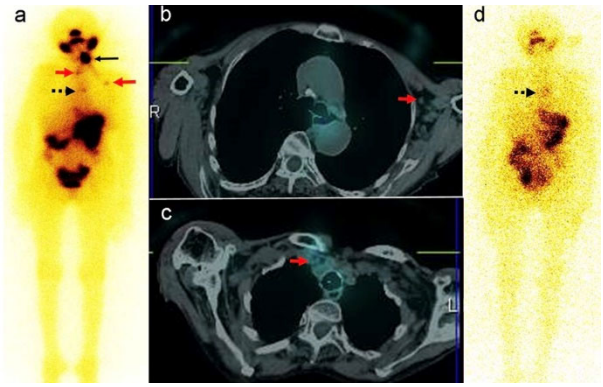

FIGURE 3 Post-therapy whole-body ^{131}I planar anterior image (a) and fused axial SPECT/CT (b,c) showing intensely tracer avid remnant (black arrow), faintly tracer avid left axillary, highest mediastinal (red arrows) and prevascular lymph nodes (broken arrow). Diagnostic whole-body ^{131}I planar anterior image (d) after 6 months showing resolution of remnant and left axillary lymph node with faint tracer uptake in the mediastinum (broken arrow)

Table 1: Cases reported for thyroid cancer with metastases to axillary lymph nodes									
Year	**Author**	**Age*/ Sex**	**Primary tumor**	**Type**	**Differentiation**	**N stage**	**Initial M stage†**	**Time to ALN detection**	**Management and outcome**
2020	Present study	69/F	R thyroid lobe 4 cm	PTC	Columnar cell	N1b	M1, R ALN, lung	Concurrent	RAI, started on thalidomide with drop in Tg
2020	Present study	70/F	L thyroid lobe 6 cm	PTC	Tall cell	N1b	M1, L ALN, Mediastinal LN	Concurrent	RAI, resolution of lesion with drop in Tg, died at 19 m
2018	Prabhu et al [6]	47/M	L thyroid lobe 3 cm	FTC	Hürthle cell	N0	M0	Recurrent 17 y	ALND, drop in Tg to 6ng/ml post-surgery
2017	Rasihashemi et al [7]	31/F	NA	MTC	-	N1b	M0	Recurrent 5 y	ALND
2015	Kamaleshwaran et al [8]	38/F	R thyroid lobe 3.8 cm	PTC	-	N1b	M1, L ALN, lungs	Concurrent	ALND, on FU
2015	Hafez et al [9]	61/M	NA	PTC	-	N1b	M0	Recurrent 1.5 y	ALND
2014	Singhal et al [10]	19/F	L thyroid lobe	PTC	Follicular	N1b	M1, L ALN, lungs	Concurrent	ALND; RAI, disease free:2m
2014	Singhal et al [10]	45/F	R thyroid lobe	PTC	Tall cell	N1b	M0	Recurrent 11 y	ALND, lung metastases, lost to FU
2015	Ozdemir et al [11]	42/M	R thyroid lobe	MTC	-	N1b	M0	Recurrent 3 y	ALND
2014	Koo et al [12]	68/M	L thyroid lobe 5.4 cm	PTC	Follicular	N1b	M0	Recurrent 17 m	ALND, drop in Tg post-surgery
2014	Cummings et al [13]	50/F	NA	PTC	-	NA	M1 lung, bone, liver	Recurrent 7 y	ALND, stable for months in follow-up.
2014	Cummings et al [13]	58/M	L thyroid lobe 1.8 cm	MTC	-	N1b	M0	Recurrent 3 m	ALND, recurrence in supraclavicular LNs, stable for 9 m
2012	Elboga et al [14]	64/M	R thyroid lobe 2 cm	PTC	Classical	NA	M0	Recurrent 14 y	ALND, seen on FGD PET/CT
2012	Chiofalo et al [15]	65/M	R thyroid	FTC	PD, signet ring	N1b	M1, R ALN,	Concurrent	ALND, RAI twice,

			lobe, 3.8 cm		cells		liver, bones		stable 1 y
2012	Machado et al [16]	69/M	R thyroid lobe 7 cm	PTC	-	N1a	M0	Recurrent 7 y	ALND, lung mets, on Sorafenib
2011	Krishnamurthy et al [17]	64/F	Thyroid swelling	PTC	-	N1b	M0	Recurrent 6 y	ALND, disease free at 6 m
2011	Damle et al [18]	37/M	L thyroid lobe	PTC	Follicular	NA	M1, lungs	Recurrent 3 y	RAI twice, resolution of ALN, drop in Tg
2010	Spector et al [19]	22/M	R thyroid lobe	MTC	PD	NA	M0	Recurrent 17 y	Liver and lymph nodes mets, stable on Sorafenib for 1.5 y
2009	Kepenekci et al [20]	63/F	L thyroid lobe 4.5 cm	PTC	-	N1b	M1, L ALN	Concurrent	ALND, NA
2009	Angeles-Angeles et al [21]	58/F	R thyroid lobe	PTC	Insular	N1b	M0	Recurrent 17 y	ALND, recurrence in left breast 3 m post-surgery, lost to FU
2007	Nakayama et al [22]	21/M	R thyroid lobe 4 cm	PTC	PD	N1b	M1, R ALN	Concurrent	ALND, recurrence at 6 y, RAI thrice, alive
2006	Ers et al [23]	62/F	L thyroid lobe 4 cm	PTC	-	N1b	M0	Recurrent 6 y	ALND, asymptomatic at 10 y follow up
2004	Shehadeh et al [24]	38/F	Thyroid swelling	SMECE	-	N1b	M1, R ALN, lung	Concurrent	Partial response with chemo-radiotherapy
2004	Koike et al [25]	46/F	NA	PTC	PD Component	N1b	M0	Recurrent 5 y	ALND, died 8 m post-surgery
2003	Lal et al [26]	59/M	R thyroid lobe 7 cm	MTC	PD	N1b	M1, L ALN, lungs	Concurrent	ALND, died at 6 m post-surgery
2002	Lal et al [27]	65/M	NA	PTC	PD	N1b	M0	Recurrent 41 y	Died at 1 m
2002	Lal et al [27]	45/F	NA	PTC	PD	N1b	M1, ALN, pericardial effusion	Concurrent	Died at 10 m
2002	Minagawa et al [28]	52/M	Goitre	MEC	-	N1b	M1, ALN, lungs, bone	Concurrent	Died at 2 m after admission

1998	Chen et al [29]	66/F	? thyroid origin	PTC	-	NA	M1, R ALN	NA	NA
1996	Ueda et al [30]	45/F	NA	PTC	-	N1b	M0	Recurrent 7 y	ALND, stable
1993	Mizukami et al [31]	57/M	R thyroid lobe, 4 cm	MAC	PD	N1b	M0	Recurrent 7 m	ALND, asymptomatic at 10 m

Abbreviations: *M: male, F: female, R: right, L: left, B/L: bilateral, NA: not available, PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, MTC: medullary thyroid carcinoma, WD: well differentiated, PD: poorly differentiated, MAC: mucin-producing adenocarcinoma, MEC: mucoepidermoid carcinoma, SMECE: sclerosing mucoepidermoid carcinoma with eosinophilia, ALN: axillary lymph node, ALND: axillary lymph node dissection, Tg: thyroglobulin, RAI: radioactive iodine. *Age at initial diagnosis of thyroid cancer. †Distant metastases at any known sites beyond head and neck soft tissues present at time of initial presentation based on available data*.

Table References:

6. Prabhu M, Jain D, Gupta SD, et al. Detection of Solitary Axillary Lymph Node Metastases from Hürthle Cell Carcinoma of the Thyroid on 18 F-FDG PET/CT. *Nucl Med Mol Imaging*. 2018;52:389-393.

7. Rasihashemi SZ, Azhough R, Ramouz A. Axillary lymph node metastasis in medullary thyroid carcinoma: A case report. *Iran J Otorhinolaryngol*. 2017;29:295-297.

8. Kamaleshwaran KK, Rajan F, Mohanan V, et al. Rare case of axillary lymph node metastasis in papillary thyroid carcinoma detected using Iodine-131 whole-body scintigraphy and single-photon emission computed tomography/computed tomography. *Indian J Nucl Med*. 2015;30:168-170.

9. Hafez MT, Refky B, Elwahab KA, et al. Axillary lymph nodes metastasis in a patient with recurrent papillary thyroid cancer: a case report. *J Med Case Rep*. 2015;9:181.

10. Singhal N, Chaturvedi P, Joshi P, et al. Axillary lymph node metastases in differentiated thyroid Cancer "an uncommon presentation with clinical implications". *Austin J Clin Case Rep*. 2015;2:1065.

11. Ozdemir M, Makay O, Simsir I, et al. Medullary carcinoma of the thyroid with axillary metastasis: a case report. *Int Surg*. 2015;100:390-393.

12. Koo EJ, Lee MR. Axillary lymph node metastasis of papillary thyroid carcinoma: a case report. *J Korean Thyroid Assoc*. 2014;7:194-200.

13. Cummings A, Goldfarb M. Thyroid carcinoma metastases to axillary lymph nodes: report of two rare cases of papillary and medullary thyroid carcinoma and literature review. *Endocr Pract*. 2014;20:e34-37.

14. Elboga U, Kalender E, Yilmaz M, et al. Axillary lymph node metastasis of papillary thyroid carcinoma detected by FDG PET/CT in a thyroglobulin-positive patient with negative whole-body 131I scan. *Clin Nucl Med*. 2012;37:1120-1122.

15. Chiofalo MG, Losito NS, Fulciniti F, et al. Axillary node metastasis from differentiated thyroid carcinoma with hürthle and signet ring cell differentiation. A case of disseminated thyroid cancer with peculiar histologic findings. *BMC Cancer*. 2012;12:55.

16. Machado NO, Chopra PJ, Raouf ZR, et al. Axillary lymph node metastasis from thyroid malignancy. Unusual presentation with ominous implications. *Br J Med Med Res*. 2013;3:1634-1635.

17. Krishnamurthy A, Vaidhyanathan A. Axillary lymph node metastasis in papillary thyroid carcinoma: report of a case and review of the literature. *J Cancer Res Ther*. 2011;7:220-222.

18. Damle N, Singh H, Soundararajan R, et al. Radioiodine avid axillary lymph node metastasis in papillary thyroid cancer: report of a case. *Indian J Surg Oncol*. 201;2:193-196.

19. Spector E, Franklin MJ, Truskinovsky AM, et al. Sorafenib induces partial response in metastatic medullary thyroid carcinoma. *Acta Oncol*. 2010;49:104-106.

20. Kepenekci I, Demirkan A, Cakmak A, et al. Axillary lymph node metastasis as a late manifestation of papillary thyroid carcinoma. *Thyroid*. 2009;19:417-419.

21. Angeles-Angeles A, Chable-Montero F, Martinez-Benitez B, et al. Unusual metastases of papillary thyroid carcinoma: report of 2 cases. *Ann Diagn Pathol*. 2009;13:189–196.

22. Nakayama H, Wada N, Masudo Y, et al. Axillary lymph node metastasis from papillary thyroid carcinoma: report of a case. *Surg Today*. 2007;37:311-315.

23. Ers V, Galant C, Malaise J, et al. Axillary lymph node metastasis in recurrence of papillary thyroid carcinoma: a case report. *Wien Klin Wochenschr*. 2006; 118:124-127.

24. Shehadeh NJ, Vernick J, Lonardo F, et al. Sclerosingmucoepidermoid carcinoma with eosinophilia of the thyroid: a case report and review of the literature. *Am J Otolaryngol*. 2004;25:48–53.

25. Koike K, Fujii T, Yanaga H, et al. Axillary lymph node recurrence of papillary thyroid microcarcinoma: report of a case. *Surg Today*. 2004;34:440-443.

26. Lal G, Brennan TV, Hambleton J, et al. Coagulopathy, marantic endocarditis, and cerebrovascular accidents as paraneoplastic features in medullary thyroid cancer-case report and review of the literature. *Thyroid*. 2003;13:601-605.

27. Lal G, Ituarte P, Duh Q, et al. The axilla as a rare site of metastatic thyroid cancer with ominous implications. Presented at: 74th annual meeting of the American Thyroid Association, October 10-13, 2002; Los Angeles, CA.

28. Minagawa A, Iitaka M, Suzuki M, et al. A case of primary mucoepidermoid carcinoma of the thyroid: molecular evidence of its origin. *Clin Endocrinol (Oxf)*. 2002;57:551-556.

29. Chen SW, Bennett G, Price J. Axillary lymph node calcification due to metastatic papillary carcinoma. *Australas Radiol*. 1998;42:241-243.

30. Ueda S, Takahashi H, Akehi S, et al. A case of recurrent thyroid cancer metastasizing to axillary lymph nodes 7 years after the initial thyroidectomy. *The Journal of the Japanese Practical Surgeon Society*. 1996;57:2934-2937.

31. Mizukami Y, Nakajima H, Annen Y, et al. Mucin-producing poorly differentiated adenocarcinoma of the thyroid: a case report. *Pathol Res Pract*. 1993;189:608-612.