Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 06, pp.17063-17065, June, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

OCCULT NEUROENDOCRINE DIFFERENTIATION IN NON-SMALL CELL LUNG CARCINOMA

***Datar, R. A., Sahu, K. K. and Pai, R. R.**

MD Pathology Datar Rujuta Anand, Flat no 10, Basav Prasad appt Basav Nagar, Belagavi, Karnataka 590010

ARTICLE INFO

Article History:
Received 05th March, 2015
Received in revised form
17th April, 2015
Accepted 05th May, 2015
Published online 27th June, 2015

Key words:

Occult neuroendocrine differentiation,
Synaptophysin,
Chromogranin.

ABSTRACT

Introduction: Neuroendocrine (NE) differentiation can be documented by immunohistochemistry (IHC) with the use of synaptophysin (SYN) and chromogranin (CGA) in some lung carcinomas with conventional non-small cell morphology. These tumors are referred as non-small cell lung carcinomas with neuroendocrine differentiation (NSCLC-ND) or non-small cell lung carcinoma with occult neuroendocrine differentiation. The finding of NE differentiation in some NSCLC has led to the hypothesis that these tumors may form a subgroup with a prognosis and response to treatment between NSCLC and SCLC. (Pelosi *et al*., 2003; Wick *et al*., 2011; Howe *et al*., 2005)
Aim: To find occult NE differentiation in NSCLC using CGA and SYN.
Materials and Methods: The IHC markers, CGA and SYN were done on 37 NSCLC cases which compromised of 23 Squamous cell carcinomas (SCC) and 14 adenocarcinomas. Semiquantitative assessments of staining intensity and percentage of tumour cells positive were made. An Intensity Distribution (ID) score of > 1 with any marker was used as the criterion for evidenceof NE differentiation.
Results: NE differentiation was seen in 40.54% of NSCLC. 50% of adenocarcinomas and 34.8% SCC showed NE differentiation. SYN and CGA positivity was seen in 29.7% and 24% NSCLCs respectively. Adenocarcinoma showed significant immunoreactivity for SYN (p=0.042) while SCC showed significant immunoreactivity for CGA (p=0.035)
Conclusion: In our study, 40.5% of NSCLC showed NE differentiation. NE differentiation was seen more in adenocarcinoma than in SCC. Synaptophysin showed significant association with adenocarcinomas and chromogranin with SCC.

***Citation*:** Datar, R. A., Sahu, K. K. and Pai, R. R. 2015. "Occult neuroendocrine differentiation in non-small cell lung carcinoma", *International Journal of Current Research*, 7, (6), 17063-17065.

INTRODUCTION

Approximately 25–33% of all lung tumors are neuroendocrine (NE) and range from relatively low-grade to intermediate-grade tumors, including typical and atypical carcinoids, to highly malignant neoplasms which include SCLC and large cell NE carcinomas (LCNEC). NE differentiation can be documented by immunohistochemistry (IHC) with the use of synaptophysin (SYN) and chromogranin (CGA) in some lung carcinomas with conventional non-small cell morphology. These tumors are collectively referred as NSCLC with neuroendocrine differentiation (NSCLC-ND). (Pelosi *et al*., 2003) They are also called as NSCLC with "occult" neuroendocrine differentiation. (Wick *et al*., 2011) These lung carcinomas, do not show neuroendocrine morphology by light microscopy, but demonstrate immunohistochemical and/or ultra structural evidence of NE differentiation.

****Corresponding author: Datar, R. A.***
MD Pathology Datar Rujuta Anand, Flat no 10, Basav Prasad appt Basav Nagar, Belagavi, Karnataka, 590010

Neuroendocrine differentiation can be shown by IHC in 10-20% of SCC, adenocarcinomas, and LCC. (Travis *et al*., 2004) In terms of treatment, the most important distinction in the diagnosis of lung carcinoma is between SCLC and NSCLC. SCLC is more chemo- and radiosensitive, but, despite this, has a worse prognosis. The finding of NE differentiation in some NSCLC has led to the hypothesis that these may form a subgroup with a prognosis and response to treatment somewhere between NSCLC and SCLC. (Howe *et al*., 2005) A broad spectrum of immunohistochemical markers can highlight NE differentiation in lung tumors, although chromogranin (CGA) and/or synaptophysin (SYN) remain the most suitable markers due to their close correlation with the ultra structural evidence of neurosecretory granules and small clear vesicles, respectively. (Pelosi *et al*., 2003)

Aims

To study incidence of occult neuroendocrine differentiation in non-small cell lung carcinomas.

MATERIALS AND METHODS

The immunohistochemical markers such as CGA and SYN were done on 37 histologically diagnosed biopsy specimens of NSCLC cases which compromised of 23 SCC and 14 adenocarcinomas. Semi quantitative assessments of staining intensity (0 = none, 1+ = weak, 2+ = moderate, 3+ = strong) and percentage of tumor cells positive (0 = none, 1+ = 33%, 2+ = 34–66%, 3+ = 67– 100%) were made. For each antibody the score for intensity was multiplied by that for distribution to give an intensity distribution (ID) score. An ID score of > 1 with any marker was used as the criterion for evidence of NE differentiation. (Howe *et al*., 2005)

RESULTS

The present study compromised of 34 males and 3 females. The mean age among carcinomas with NE differentiation was 63.6 years. There was male preponderance with M:F::6.5:1. NE differentiation was seen in 15 out of 37 NSCLC cases (40.54%) and was absent in 22 cases (59.45%).

Table 1 shows ID scores for each antibody. Positive was defined as staining in excess of focal weak (ID score > 1). SYN was positive in 11 NSCLC cases amounting 29.7% and CGA was positive in 9 NSCLC cases amounting to 24.3%. Overall 40.54% cases of NSCLC showed NE differentiation.

Table 1. Intensity-distribution scores for each antibody

ID Score	SYN	CGA
0	27.02%	35.13%
1	43.24	40.54%
2	27.02%	16.21%%
3	0	2.70%
4	2.70%	5.40%
6	0	0
9	0	0

NE differentiation with cell type is shown in Table 2. In the present study, 8 (34.8%) cases out of 23 SCC showed positivity for either of the IHC markers SYN and CGA. 7 (50%) cases out of 14 adenocarcinoma showed positivity for either of the IHC markers SYN and CGN. Of the 11 positive cases of SYN, 7 (63.66%) cases were adenocarcinomas and 4 (36.36%) cases were SCC. Adenocarcinoma showed significant positivity for synaptophysin (p=0.035). Of the 9 positive cases of CGA, 1 (11.11%) case was of adenocarcinoma and 8 (88.89%) cases were of SCC. SCC showed significant positivity for CGA (p=0.042).

Table 2. Neuroendocrine (NE) positivity related to NSCLC subtype

	SCC	Adenocarcinoma
NE +	34.8%	50%
NE -	65.2%	50%

DISCUSSION

Comparison of age and sex distribution is shown in Table 3. The mean age in our study was 63.6 years which was comaprable to other studies. (Howe *et al*., 2005; Hiroshima *et al*., 2002) The M: F ratio was 6.5:1 showing definite male preponderance. Previous studies (Howe *et al*., 2005; Hiroshima *et al*., 2002) have shown equal incidence among both the sexes with slight male preponderance. Comparison of Neuroendocrine differentiation among different studies is shown in Table 4. In the present study, Neuroendocrine positivity for either markers was 40.54%. Our findings were comparable to Howe *et al*. (2005) who reported NE differentiation in 36% of NSCLC. Graziano *et al*. (1994) reported 10-70% NE differentiation in NSCLC using Neuron specific enolase, Leu-7, CGA and SYN. Some studies (Ionescu *et al*., 2007; Berendsen *et al*., 1989) have found a low number of NSCLC's showing NE differentiation (13.6%).

Table 3. Comparison of Age and sex incidence among different studies

	Howe *et al*. (2005)	Hiroshima *et al*. (2002)	Present study
No of cases	98	90	37
Age	62	65	63.6
Sex ratio	1:1.82	1: 1.33	6.5:1

Table 4. Comparison of Neuroendocrine differentiation among different studies

	Howe *et al*. (2005)	Ionescu *et al*. (2007)	Graziano *et al*. (1994)	Berendsen *et al*. (1989)	Present study
NE differentiation	36%	13.6%	10-70%	30%	40.54%

Table 5. Comparison of Neuroendocrine markers positivity among different studies

	Howe *et al*. (2005)	Ionescu *et al*. (2007)	Sundaresan *et al*. (1991)	Present study
SYN	17.6%	7.5%	23%	29.7%
CGA	1%	0.4%%	7%	24.32
NCAM	28%	8.6%	-	-
NSE	-	-	57%	-
Other markers (CKBB+BLP+NT+UJ-13A)	-	-	48%	-

Table 6. Comparison of Intensity distribution score of Synaptophysin among different studies

	Howe *et al*. (2005)	Present study
0	72.1%	27.02%
1	10.3%	43.24%
2	8.2%	27.02%
3	5.2%	0
4	2.1%	2.70%
6	2.1%	0
9	0	0

Table 7. Comparison of Intensity distribution score of Chromogranin among different studies

	Howe *et al*. (2005) (%)	Present study (%)
0	91.8	35.13
1	7.2	40.54
2	1	16.21
3	0	2.70
4	0	5.40
6	0	0
9	0	0

Comparison of Neuroendocrine markers positivity among different studies is shown in Table 5. In the present study out of

37 NSCLC, 29.7% and 24.3% of cases were positive for SYN and CGA respectively. Immunostaining for SYN was more compared to CGA immunoreactivity. Adenocarcinoma showed significant positivity for synaptophysin (p=0.035) while SCC showed greater positivity for CGA (p value=0.042). Our study findings correlated well with all the above studies (Howe *et al*., 2005; Ionescu *et al*., 2007; Sundaresan *et al*., 1991) where SYN showed more positivity than CGA. Howe *et al*. (2005) reported SYN, CGA and NSE immunostaining in 17.2% 1% and 28% of tumors respectively. Furthermore they found NCAM showed higher positivity for SCC as compared to SYN. Ionescu *et al*. (2007) reported 7.5%, 0.4% and 8.6% immunoreactivity for SYN, CGA and NCAM respectively. They found that SNP is more likely to be expressed in adenocarcinoma (P=0.01) and N-CAM in SCC (P=0.008). Similar to our study, Pelosi G *et al*[1] found SCC showed more CGA immune reactive cells compared with adenocarcinomas (*P* =0.015).

Table 6 and 7 show comparison of intensity distribution score of SYN and CGA respectively among different studies. In a study by Howe *et al* (2005) they found positive ID score of 2, 3, 4, 6 and 9 for SYN in 8.2%, 5.2%, 2.1%, 2.1% and 0% cases respectively. In present study, positive ID score for SYN of 2,3, 4, 6 and 9 was seen in 27.02%, 0%, 2.70%, 0% and 0% respectively. For CGA, Howe *et al*. (2005) found positive intensity distribution of 2 in 1% cases. None of the cases showed ID score of 3 and above. In present study, positive ID score of 2, 3 and 4 was seen in 16.21%, 2.70% and 5.40% respectively. None of the cases showed ID score of 6 and 9. In our study 50 % of adenocarcinoma and 34.8% SCC showed NE differentiation. There was greater proportion of NSCLC-ND in adenocarcinoma. Similar results were found in a previous study[1] which reported NE differentiation in 17% adenocarcinoma and 13 % SCC.

Poorly differentiated adenocarcinomas and undifferentiated LCC showed the highest percentage of positive samples (30%-60%) with diffuse and intense immune staining. Poorly differentiated SCC, bronchioalveolar adenocarcinomas, and giant cell carcinomas showed a lower percentage of positive samples (20%) with moderate immune staining. (Baldi *et al*., 2000) Similar results of adenocarcinoma showing greater proportion of NE differentiation were reported in other studies. (Graziano *et al*., 1994; Berendsen *et al*., 1989) No difference in NE differentiation between cell types was reported in one of the previous studies (Howe *et al*., 2005)

Conclusion

In present study we found 40% of NSCLC showed NE differentiation. The findings of present study suggest that NE differentiation is seen more in adenocarcinoma than in SCC. Synaptophysin shows significant association with adenocarcinomas and chromogranin with SCC.

REFERENCES

Baldi A, Groger AM, Esposito V, Di Marino MP, Ferrara N, Baldi F. Neuroendocrine differentiation in non-small cell lung carcinomas. *In Vivo*. 2000;14:109–14.

Berendsen H, DeLeij L, Poppema S *et al*. Clinical characterization of non-small-cell lung cancer tumors showing neuroendocrine differentiation features. *J ClinOncol*., 1989; 7:1614–20.

Graziano SL, Tatum AH, Newman NB *et al*. The prognostic significance of neuroendocrine markers and carcinoembryonic antigen in patients with resected stage I and II non-small cell lung cancer. *Cancer Res*., 1994; 54:2908-13.

Hiroshima K, Iyoda A, Shibuya K, Toyozaki T, Haga Y, Fujisawa T *et al*. Prognostic significance of neuroendocrine differentiation in adenocarcinoma of theLung. *AnnThorac Surg*., 2002;73:1732-5.

Howe M C, Chapman A, Kerr K, Dougal M, Anderson H, Hasleton P S. Neuroendocrine differentiation in non-small cell lung cancerand its relation to prognosis and therapy. *Histopathology*, 2005;46:195–201.

Ionescu DN, Treaba D, Gilks CB, Leung S, Renouf D, Laskin J *et al*. Non small cell lung carcinoma with neuroendocrine differentiation-an entity of no clinical or prognostic significance. *Am J SurgPathol*., 2007;31(1):26-32.

Pelosi G, Pasini F, Sonzogni A, Maffini F, Maisonneuve P, Iannucci A, *et al*. Prognostic implications of neuroendocrine differentiation and hormone production in patients with stage I non small cell lung carcinoma. *Cancer*, 2003; 97(10):2487-97.

Sundaresan V 2, Reeve JG, Stenning S, Stewart S, Bleehen NM.Neuroendocrine differentiation and clinical behaviour in non-small cell lung tumours. *Br J Cancer*, 1991;64: 333-8.

Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, editors. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: *International Agency for Research on Cancer*, 2004.

Wick MR, Allen TC, Leslie KO, Ritter JH, Mills SE. Neuroendocrine lesions of the lung. In: Leslie KO, Wick MR, editors. Practical pulmonary pathology. 2nd ed. Philadelphia: saunders; 2011. p. 329-30.

****