



CD44 AND CD117 EXPRESSION IN DIFFERENTIATING NON SMALL CELL LUNG CARCINOMA AND SMALL CELL LUNG CARCINOMA

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ABSTRACT

Lung carcinoma is one of the leading cause of cancer related deaths worldwide. According to WHO classification it is divided broadly on the basis of origin- epithelial(non small cell carcinoma and small cell carcinoma), mesenchymal, lymphohistiocytic and ectopic origin. Histopathological examination using routine H and E staining is the basic step for diagnosis of lung carcinoma. Due to emerging subtypes of lung carcinoma, problems faced with biopsies (size, artifacts etc) and nature of tumor, it is required for early and accurate diagnosis even with less tissue. Thus, immunohistochemistry plays important role in not only diagnosing but also differentiating between various subtypes. Along with already proven panel of biomarkers like TTF-1, p63 for non small cell carcinoma and chromogranin and CD56 for small cell lung carcinoma, two new biomarkers CD44 and CD117 also help in not only diagnosing but also differentiating between these two carcinomas.

KEYWORDS: immunohistochemistry, biomarkers, lung carcinoma.

INTRODUCTION

Non small cell lung carcinoma constitutes 85% of total lung carcinoma and is further divided mainly into squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Small cell carcinoma constitutes 15% of total lung carcinoma. These are the result of multiple complex combinations of morphological, molecular and genetic alterations which lead to imbalance between tumor suppressor genes and tumor promoter genes which in turn leads to cells with malignant potential. The most widely used adenocarcinoma markers include mucin (periodic acid Schiff with diastase or mucicarmine), TTF-1 (thyroid transcription factor 1) and napsin-A, and for SCC the favoured markers are p63 and CK5/6. Of these, TTF-1 and p63 demonstrate the greatest sensitivity for their respective NSCLC subtypes. Markers for small cell carcinoma includes chromogranin, CD56, synaptophysin, NSE etc. Along with them, CD44 and CD117 can be used to diagnose and differentiate between non small cell and small cell lung carcinoma.

CD44 is 90-kd transmembrane glycoprotein that is widely distributed on the surface of T cells, granulocytes, monocytes, fibroblasts, keratinocytes and epithelial cells and is involved in various cell adhesion events including lymphocyte migration, hematopoiesis and tumor

metastasis. It belongs to polymorphic family of cell surface glycoproteins that function as receptor for the extracellular matrix, glycan, hyaluronan, it has cytoplasmic domain, 7 extracellular domains and a transmembrane domain. CD44 has been accepted as excellent prognostic indicator in solid tumors including non small cell lung carcinoma and it was revealed to be a target of Wnt pathway which is accepted as key pathway for stemness confined to surface of bronchial basal cells and alveolar macrophages. CD117-Kit is a type III receptor tyrosinase-kinase, operating in cell signal transduction in several cell types. It is encoded by the c-kit gene that is located on the human chromosome segment 4q11. The loss of function mutations have demonstrated the crucial role of c-kit in normal growth and/or differentiation of several types. Normally Kit is activated (phosphorylated) by binding to its ligand, the stem cell factor. This leads to a phosphorylation cascade, ultimately activating various transcription factors in different cell types. Such activation regulates apoptosis, cell differentiation, proliferation, chemotaxis and cell adhesion.

OBSERVATIONS AND RESULT

We studied 60 cases of primary lung carcinoma, 30 each of non small-cell and small cell carcinoma diagnosed on

routine H & E staining. Along with primary panel of biomarkers like TTF-1, p63, CD56 and chromogranin, CD44 and CD117 were also applied on all 60 cases. Out of 30 cases of non small cell carcinoma 22 were subtyped as squamous cell carcinoma and 8 as adenocarcinoma. Age range in our study was 31-90 years. Mean age in our study was 62 years (61.96). Maximum number of patients were in age group of 61-70 years(40%) followed by age group 51-60 years(23.33%). There was no case below age of 30 years and above 90 years. Maximum number of patients of non small-cell lung carcinoma and small cell lung carcinoma lied in the age group of 61-70 years. Male: female ratio was 5:1, where males comprised 83.33% and females comprised 16.66%. Number of males was more in both non small cell lung carcinoma and small cell lung carcinoma (45% and 38% respectively) than females (5% and 11% respectively). CD44 was positive in 17 (77.27%) cases of squamous cell carcinoma and 7(87.5%) cases of adenocarcinoma. Diagnostic accuracy of CD44 was 81.67%. Out of 24 positive cases for CD44, in 20 cases,

cells. CD117 was found to be positive only in 1 case and that too of squamous cell carcinoma. Thus its diagnostic accuracy in NSCLC was 11.67%. Out of all TTF-1 positive cases (8) of adenocarcinoma, CD44 was positive in 7 cases and out of 6 of 22 positive cases of squamous cell carcinoma, CD44 was positive in 5 cases. Out of 8 cases of adenocarcinoma, p63 was positive in 2 cases and CD44 was also positive in both the cases and of 21 positive cases of squamous cell carcinoma CD44 was positive in 16 cases.

CD117 was positive in 24(80%) of 30 cases of small cell carcinoma, thus its diagnostic accuracy was 83.33%. CD44 was found to be positive in 5(16.66%) of 30 cases of small cell carcinoma with diagnostic accuracy of 18.33%. Out 25 cases which were positive for chromogranin, CD117 was positive in 21 cases and CD44 was positive in 4 cases. Out of 28 positive cases for CD56, CD117 was positive in 23 cases and 1 was positive for CD44.

Table 1: Histological subtype of lung carcinoma biopsy proven (n= 60)

Lung carcinoma	No of cases (n=60)	Percentage%
Non small cell carcinoma(n=30)		
Squamous type	22	36.66
Adenocarcinoma	8	13.33
Total	30	50
Small cell carcinoma(n=30)	30	50

Table 2: CD44 status in lung carcinoma (n= 60)

Lung carcinoma	CD44	sensitivity	specificity	PPV	NPV	P value
NSCLC (n=30)						
POSITIVE	24 (80%)	80%	83.33%	82.80%	80.60%	<0.001
NEGATIVE	6 (20%)					
SCLC (n=30)						
POSITIVE	5 (16.66%)	16%	20%	17.20%	19.40%	<0.001
NEGATIVE	25 (83.33%)					

Table 3: CD117 status in lung carcinoma (n=60)

Lung carcinoma	CD117	sensitivity	specificity	PPV	NPV	P value
NSCLC(n=30)						
Positive	1 (3.33%)	3.30%	20%	4%	17%	<0.001
Negative	29					

	(96.66%)					
SCLC(n=30)						
Positive	24 (80%)	80%	96.7%	96%	82.9%	<0.001
Negative	6 (20%)					

DISCUSSION

According to WHO criteria, cases of non small cell lung carcinoma were further divided into squamous cell carcinoma, adenocarcinoma. Diagnostic criteria taken into account for squamous cell carcinoma was

keratinisation, intercellular bridging and criteria for adenocarcinoma was gland formation mucin production. Considering this criteria, out of 30 cases of non small cell carcinoma 8 were of adenocarcinoma and 22 were of squamous cell carcinoma.

Table 1: CD44 status in NSCLC and SCLC in current study (n=30)

S. no.	Squamous cell carcinoma(n=22)	Adenocarcinoma(n=8)	Total	Small cell carcinoma(n=30)
CD44+	17(77.27%)	7(87.5%)	24(80%)	5(16.66%)
CD44-	5(22.72%)	1(12.5%)	6(20%)	25(83.33%)

In current study out of 22 cases of squamous cell carcinoma 17 cases(77.27%) and 7 cases(87.5%) of

adenocarcinoma showed CD44 positivity. In small cell carcinoma only 16.66% cases showed CD44 positivity.

Table 2: Comparison of CD44 status in non small cell lung carcinoma.

S. No	Name of study	No. of cases of NSCLC	Method	CD44 + Squamous	CD44+ Adenocarcinoma
1	Ronald R. Fiscus et al	123	IHC	21/27(77.77%)	41/96(42.7%)
2	Nagio T. et al	43	IHC	15/19(79%)	5/23(22%)
3	Roudi R et al	135	IHC	59/74(79.7%)	27/61(44.2%)
4	Margret B et al	11	IHC	6/8(75%)	3/3(100%)
5	Bo Hu et al	93	IHC	51/72(70.8%)	10/19(52.6%)
6	Zhuang Luo et al	43	IHC	14/24(58.33%)	13/19(68.4%)
7	Hirata T et al	68	IHC	13/25(52%)	1/43(2.3%)
8	Current study	30	IHC	6/22(27.27%)	8/8(100%)

All the studies mentioned above show CD44 positivity more in squamous cell carcinoma as compared to adenocarcinoma except studies conducted by Zhang Luo et al and Margret B et al which shows CD44 positivity

more in adenocarcinoma as compared to squamous cell carcinoma which is in concordance with our study. CD44 expression in NSCLC in our study had p value<0.001.

Table 3: Comparison of CD44 status in small cell lung carcinoma.

S. No	Name of study	No. of cases of SCLC	CD44+
1	Margret B. et al	9	0(0%)
2	Roudi R et al	37	2(5.4%)
3	Current study	30	5(16.66%)

Table 4: CD117 status in small cell carcinoma and non small cell carcinoma in current study (squamous cell carcinoma and adenocarcinoma)

Marker	Small cell carcinoma(n=30)	Squamous cell carcinoma(n=22)	Adenocarcinoma(n=8)
CD117+	24(80%)	1(4.5%)	0(0%)
CD117-	6(20%)	21(95.45)	8(100%)

CD117 status in small cell lung carcinoma showed 24 cases(80%) positive and only 3.44% cases of non small cell carcinoma positive.

Table 5: Comparison of CD117 in small cell lung carcinoma.

S no.	Name of study	No. of SCLC cases	Method	CD117+
1	Kelly J et al	11	IHC	9(82%)
2	Clark MD Steven et al	30	IHC	16(53.33%)
3	Giulio R et al	27	IHC	21(77.77%)
4	Laura B et al	60	IHC	55(91.66%)
5	Potti A et al	223	IHC	75(33.6%)
6	Fuyou Z. et al	39	IHC	34(88%)
7	Current study	30	IHC	24(80%)

All the studies mentioned above and studies conducted by Pelosi et al (67-80% positive cases) and Casali et al(61% positive cases) showed significant expression of

CD117 in small cell carcinoma. In our study also CD117 showed 80% expression in SCLC with $p < 0.001$.

Table 6: Comparison of CD117 in non small cell lung carcinoma.

S no.	Name of study	No. of cases of NSCLC	Method	CD117+
1	Kelly J et al	45	IHC	11(26%)
2	Giulio R et al	48	IHC	0
3	Tomohiko S et al	99	IHC	17(17.17%)
4	Current study	30	IHC	1(3.33%)

CONCLUSION

Though routine H and E staining is the basic step for diagnosing primary lung carcinoma, immunohistochemical markers aid not only in diagnosing but also differentiating between subtypes of

lung carcinoma. Apart from primary panel of biomarkers for NSCLC and SCLC individually, CD44 and CD117 can also be used to assess and differentiate between these two lung carcinomas and provide further subtyping in non small cell lung carcinoma.

PICTOGRAPHS

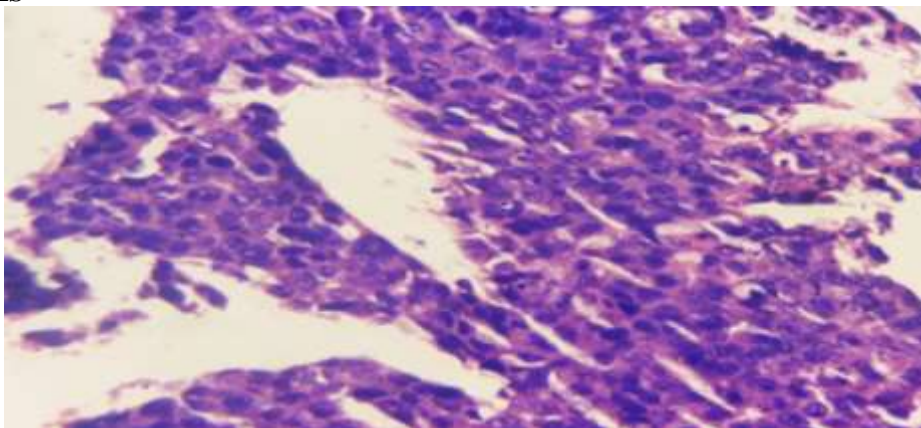


Fig 1: squamous cell carcinoma-pleomorphic squamous cells arranged in sheets(HE,40X)

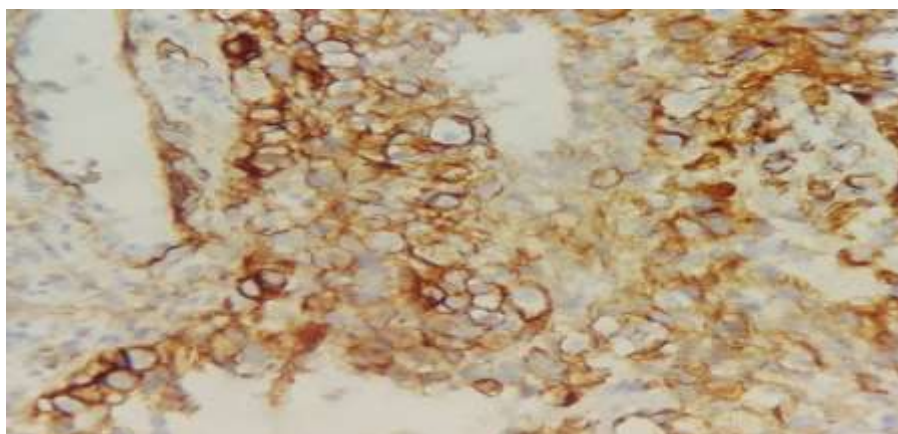


Fig 2: Membranous positivity CD44 (40X)

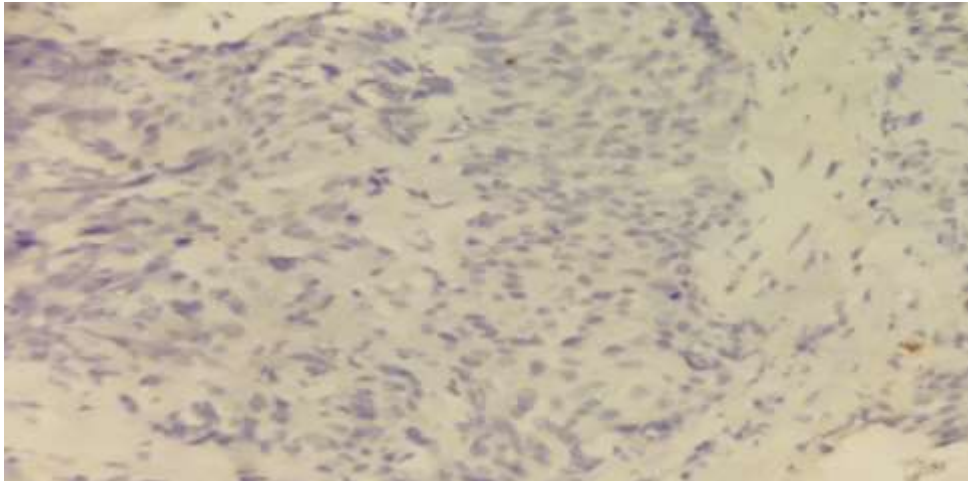


Fig 3: Negative expression of CD117 (40X)

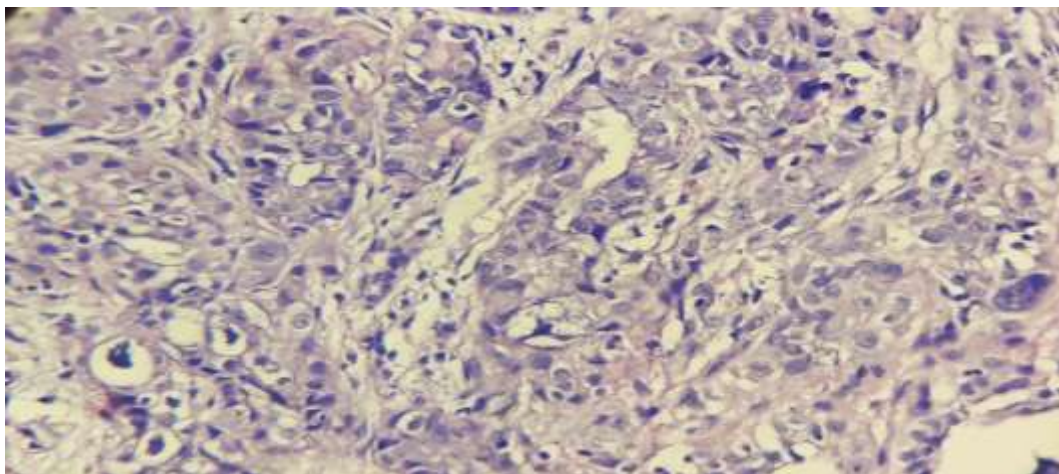


Fig 4: Adenocarcinoma- atypical cells forming glands(HE, 40X)

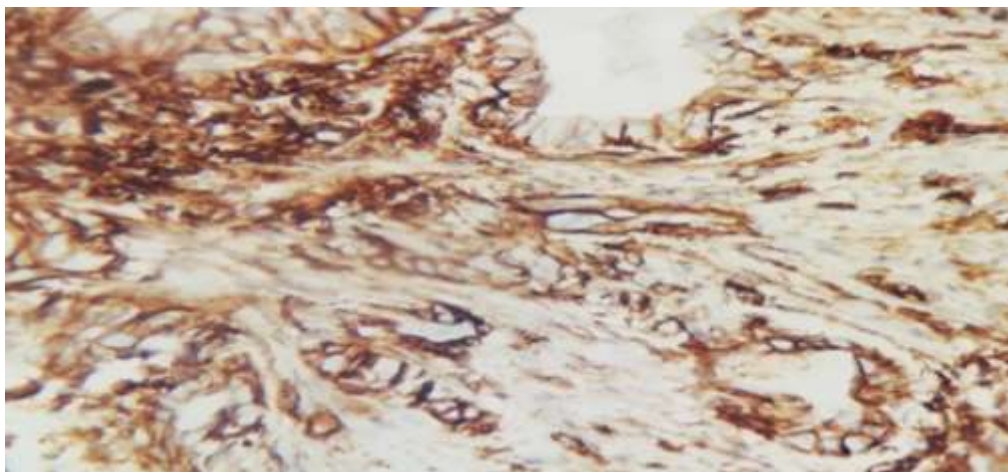


Fig 5: Membranous positivity CD44(40X)

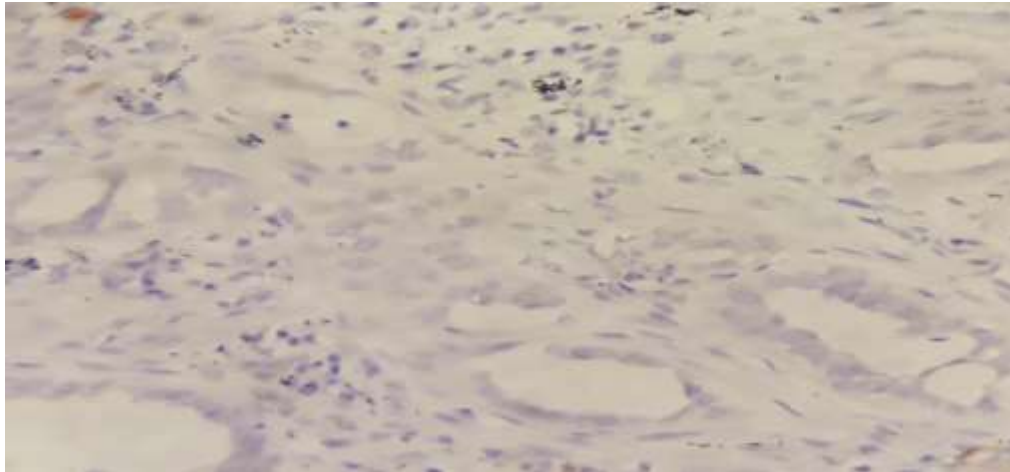


Fig 6: Negative expression of CD117(40X)

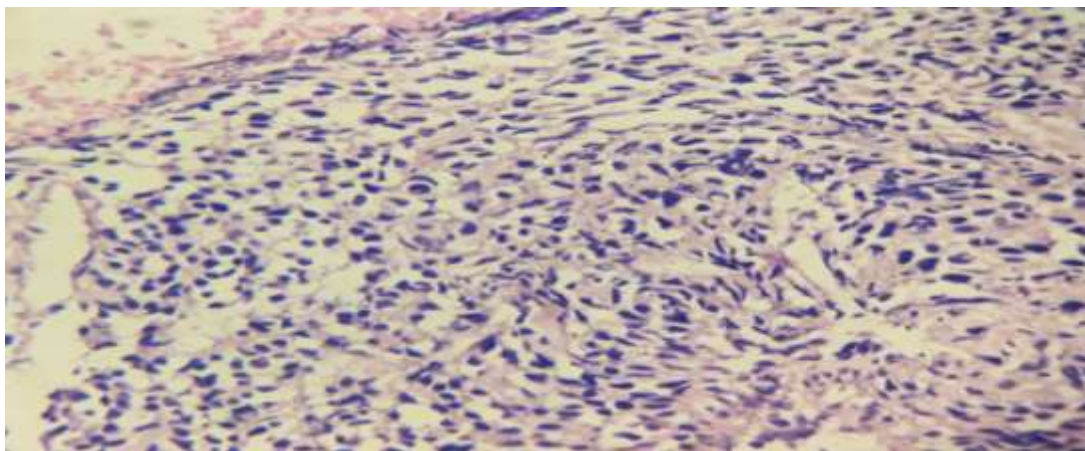


Fig 7: Small cell carcinoma- round blue cells in sheet (HE,40X)

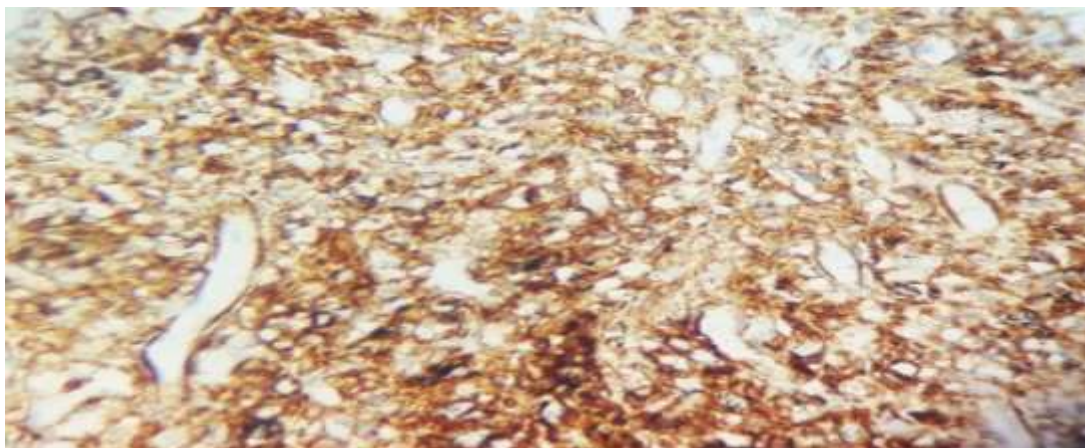


Fig 8: Membranous positivity CD117 (40X)

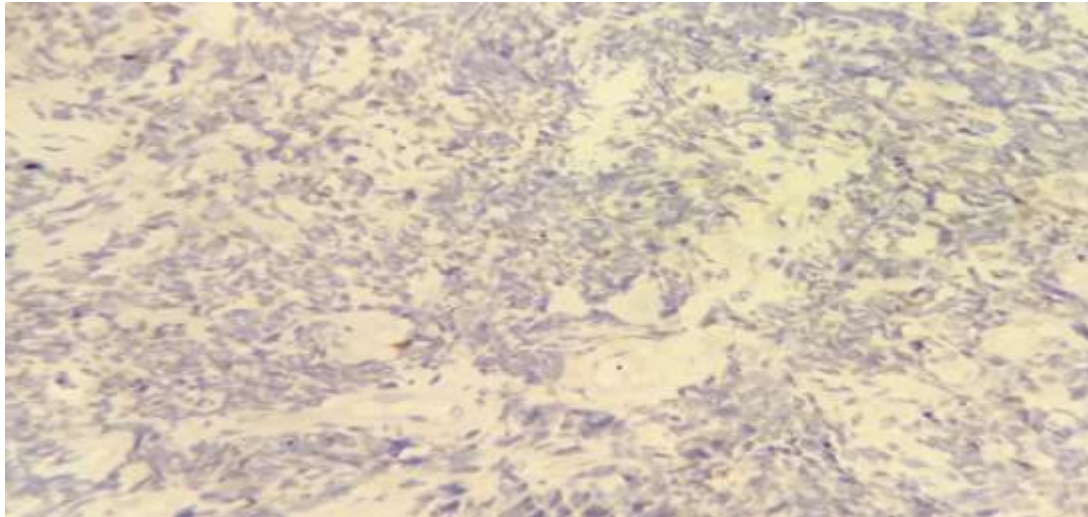


Fig 9: Negative expression of CD44(40X)

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