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Original Research Article

Cytohystological and immunohistochemical correlation of cutaneous neoplastic lesions: Three year retrospective study

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ABSTRACT

Background: Neoplastic lesions in cutaneous and subcutaneous region comprise a large group of benign and malignant entities of different lineage. Clinical, morphological features and prognosis of these lesions differ a lot. For diagnosis FNAC (Fine needle aspiration cytology) is the first technique applied followed by histology, immunohistochemistry (IHC) and so on.

Aim: Cytological evaluation of cutaneous and subcutaneous neoplasms and correlate with histopathology and IHC.

Settings and Design: Study of all palpable cutaneous and subcutaneous swellings presenting to cytology OPD (Out patient department) with further histopathological correlation in the three-year duration.

Materials and Methods: FNA cytospreads of the cases stained with leishman stain in most of cases. Histopathological and IHC correlation done in available cases.

Statistical Analysis: The data are expressed in descriptive statistics measures such as percentages and proportions.

Results: Out of 1032 total cases, most of the cases were benign (94.3%) with fewer malignant cases (5.7%). Lipomas 562(56.31 %) were the largest group among benign lesions followed by benign spindle cell lesions 286(28.65%). Metastatic (22, 64.7%) lesions were more in number than primary cutaneous malignancies (12,35.2%). Among adenocarcinomas, 4 metastatic cases (0.38%) from lung and breast each and among squamous cell carcinomas (SCC), 7(0.67%) primary SCC were seen. Biopsy correlation was available in 134(12.98%) cases and IHC done in 14(1.35%) cases.

Conclusion: Cutaneous neoplasms though benign in most of the cases, can be of critical aetiology with dismal prognosis. Hence they should not be taken lightly and diagnosed specifically with the help of imaging and cyohistological study whenever needed.

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1. Introduction

Neoplastic lesions in skin and subcutaneous tissue can be incidental findings or associated findings in previously diagnosed cases. They are categorised as benign or malignant, primary or metastatic, epithelial or mesenchymal. They have a broad range of clinical presentations and morphological variations. As they differ

in size, shape, colour, location, number, rate of growth, associated symptoms, histomorphology etc; diagnosis of these entities are quite challenging for both clinicians and pathologists many times.¹Cytological study only is inadequate for diagnosis and management in large number of cases requiring further histopathological and immunohistochemical follow up.

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2. Materials and Methods

This is a three year retrospective study carried out in our department of pathology from January 2017 to December 2019. During this period all palpable skin lesions advised for FNAC were included in the study of all age groups and both sexes. In all 1032 cases detail clinical history and other investigational findings were collected from records. FNAC had been performed using 22 to 24 Gauge needle with aseptic precautions. Cytosmears of Leishman, Hematoxylin & Eosin (H&E) and papanicolaou stain were available. The lesions were categorised into benign and malignant lesions. Histological and immunohistochemical correlation was done whenever available. Inclusion criteria for our study were cytologically all cutaneous lesions diagnosed as benign or malignant of both epithelial or mesenchymal origin. Exclusion criteria were nonneoplastic inflammatory lesions, sites other than skin and guided FNAC cases.

2.1. Statistical analysis

The data were expressed in descriptive statistics measures such as percentages and proportions.

3. Results

The study included a total number of 1032 cases comprising of 582(56.39%) males and 450(43.60%) females. Maximum patients belonged to age group 31-40 yrs. Male female ratio was 1.29: 1.[Table 1]

Most common benign neoplastic lesions were lipoma. Maximum cases of lipomas seen in upper extremity followed by trunk. Benign spindle cell lesions were the second most frequent category of lesions, mostly encountered in upper extremity [Figure 1A-F]. Appendageal tumors and vascular lesions seen in head and neck region mostly [Table 2][Figure 2A,B].

Among neoplastic cutaneous and subcutaneous lesions maximum adenocarcinomatous deposits were seen in trunk (chest wall). Squamous cell carcinomas more frequent in head and neck region. Single case of plasmacytoma seen in anterior chest wall [Figure 3 A-D] [Table 3].

Both epithelial and mesenchymal lesions of benign category outnumbered (94.3%) their malignant counterpart. Adenocarcinomas were the most common metastatic malignancies whereas squamous cell carcinomas were the largest group of primary cutaneous malignancies [Figure 4 A-D]. On cytohistological correlation lipomas and GCT tendon sheath were correct on histological diagnosis most of times. Two malignant appendageal tumors were diagnosed as metastatic deposits in cytology. One neural tumor case on histology was confirmed as appendageal tumor chondroid syringoma. Both benign and malignant spindle cell lesions along with metastatic deposits had wide array of histological diagnosis [Tables 4 and 5][Figure 5 A-C].

Metastatic (22, 64.7%) lesions were more than primary cutaneous malignancies(12,35.2%) in our study. Trunk(chest wall) was the most common site of metastasis. One SCC was found to be granular cell tumor on histopathological study. Two metastatic deposits high grade cases in cytology were rediagnosed as BCC.

Out of 1032 cytologically diagnosed cases only in 134(12.98%) cases further histopathological study and in mere 14(1.35%) cases immunological study was undertaken. Six out of 12 adenocarcinoma cases were confirmed on histology and IHC, among which four cases belonged to lung and breast each. In our study metastatic deposit from lung malignancy were found to be equal to breast. Out of four cases of lung malignancy one was diagnosed as small cell carcinoma [Table 6].

4. Discussion

Cutaneous malignancies, whether primary or secondary, benign or malignant of any lineage may present with unpredictable varied clinical presentation and in different age groups with no gender predilection. This uncertainty makes it more difficult to diagnose and manage early many a times.

In our study patients age ranged from 2-86 yrs. Similar wide age groups have been observed by various authors.^{2,3} Male female ratio was 1.29: 1 with male preponderance. Goutam et al have reported ratio of 1.40:1.³ Most common benign neoplastic lesions in current study were lipomas. Similar findings have been reported by other authors.^{2,4} Lipomas can be superficial or deep in location. Superficial lipomas constitute 16%–50% of soft-tissue tumors. Deep intramuscular lipomas can acquire a larger size.⁵ Benign spindle cell lesions were the second most frequent category of lesions, echoing study by Goutam et al.³ They were mostly seen in upper extremity similar to study by Jain et al.⁶ On histological study wide array of lesions were diagnosed namely BFH, desmoid tumor, fibromatosis, DFSP and nodular fasciitis highlighting the importance of biopsy and immunohistochemical studies needed in such cases. DFSP are seen most commonly in the trunk. But in our study upper extremity was the most affected site. Patients usually present with either an indurated plaque or ulcerated nodule. Local recurrence after surgery is common.⁷ Nodular fasciitis presented as painful lesion in upper extremity in our study similar to other authors.⁸ Appendageal tumors were mostly located in head & neck region in current study. Histology helped in specific diagnosis of pilomatricoma, nodular hidradenoma, cylindroma, chondroid syringoma, syringocystadenoma papilliferum, sebaceous adenoma and sebaceous carcinoma. Skin appendageal tumours often are cause of diagnostic difficulties due to differing clinical picture and similar morphology. Some of them can turn malignant and some may be associated with syndromes like Muir-Torre

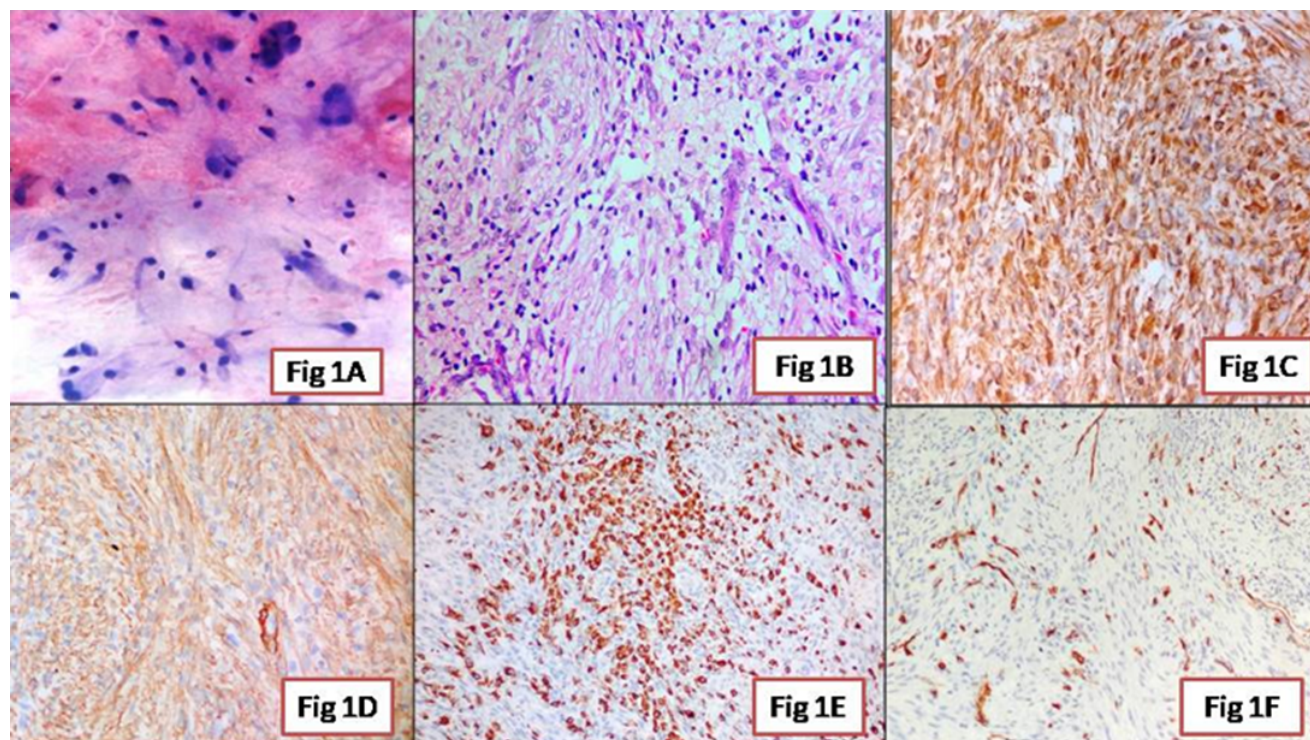


Fig. 1: **A:** FNA cytospin show benign scattered spindle cells,Leishman stain,X100; **B:** Fibrohistiocytic lesion,H&E stain,X100, H&E stain,X100; **C,D:** Cytoplasmic vimentin and desmin positive,IHC,x100; **E:** CD68 positive cluster of cells,IHC,X100; **F:** CD34 positive in blood vessels,IHC,X100

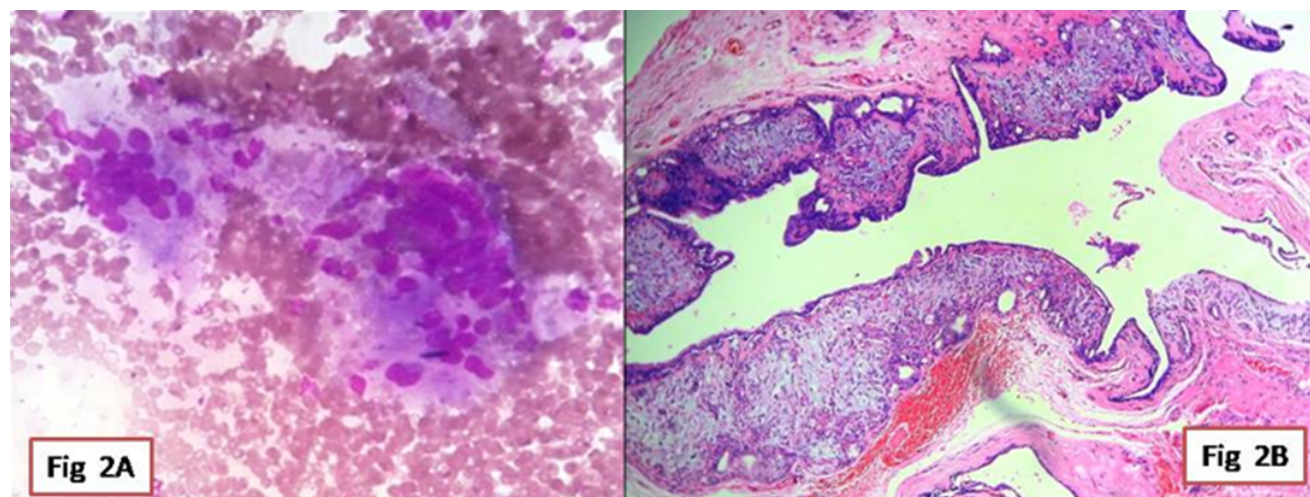


Fig. 2: **A:** Cluster of benign epithelial cells in hemorrhagic background, Leishman stain,X100; **B:** Chondroid syringoma, H&E stain,X100

Table 1: Age and gender distribution

Age	Male (No, %)	Female (No, %)	Total
1 to 10	22(2.13 %)	12(1.16 %)	34(3.29 %)
11 to 20	28(2.71 %)	18(1.74 %)	46(4.45 %)
21 to 30	118(11.43%)	96(9.30 %)	214(20.7 %)
31 to 40	211(20.44 %)	198(19.18%)	409(39.63%)
41 to 50	66(6.39 %)	37(3.58 %)	103(9.98 %)
51 to 60	62(6.0 %)	37(3.58 %)	99(9.59 %)
61 to 70	35(3.39%)	24(2.32 %)	59(5.71 %)
71 to 80	25(2.42 %)	14(1.35 %)	39(3.77 %)
81 to 90	15(1.45 %)	14(1.35%)	29(2.81 %)
Total	582 (56.39%)	450 (43.60%)	1032 (100 %)

Table 2: Distribution of benign neoplastic cases as per site

	Head & neck	UE*	LE**	Trunk	Back	Total
Lipoma	65(6.51%)	219(21.9%)	19(19.03%)	205(20.5%)	54(5.4%)	562(56.31 %)
Benign Spindle Cell Tumor	14(1.4%)	143(14.3%)	74(7.41 %)	28(2.8 %)	27(2.7%)	286(28.65%)
Appendageal Tumor	28(2.8%)	15(1.5%)	3(0.03%)	4(0.04%)	3(0.03%)	53(5.31 %)
Vascular Lesion	25(2.5%)	3(0.03%)	5(0.05%)	14(1.4%)	6(0.06%)	53(5.31%)
Neural Tumor	0	5(0.05%)	3(0.03%)	6(0.06%)	2(0.02%)	16(1.6 %)
GCT Tendon Sheath‡	0	26(2.6%)	2(0.02%)	0	0	28(2.8 %)
Total	132(13.2%)	411(41.1%)	106(10.6 %)	257(25.7%)	92(9.21%)	998(100%)

*UE: Upper Extremity, **LE: Lower Extremity, ‡GCT: Giant cell tumor

Table 3: Distribution of malignant neoplastic cases as per site

	Head & neck	UE	LE	Trunk	Back	Total
Adenocarcinoma	2(5.88%)	2(5.88%)	1(2.94%)	4(11.76%)	2(5.88%)	11(32.35%)
SCC	5(14.7%)	2(5.88%)	2(5.88%)	0	0	9(26.4%)
Undifferentiated Tumor	1(2.94%)	1(2.94%)	1(2.94%)	0	0	3(8.82%)
BCC*	2(5.88%)	0	0	0	0	2(5.88%)
Melanoma	0	1(2.94%)	2(5.88%)	0	0	3(8.82%)
Pleomorphic Sarcoma	0	1(2.94%)	1(2.94%)	0	0	2(5.88%)
Synovial Sarcoma	0	0	1(2.94%)	0	0	1(2.94%)
Metastatic Germ Cell Tumor	0	0	1(2.94%)	0	0	1(2.94 %)
Granular Cell Tumor	0	0	0	1(2.94%)	0	1(2.94%)
Plasmacytoma	0	0	0	1(2.94%)	0	1(2.94%)
Total	10(29.41%)	7(20.58%)	9(26.4%)	6(17.6%)	2(5.88%)	34(100%)

*BCC: Basal cell carcinoma

syndrome, Brooke-Spiegler syndrome etc.⁹ GCT tendon sheath and lipoma on cytohistological correlation were correct most of times, proving histology study not essential in some cases. GCT can be benign or malignant and seen in any age group. The lesions are located in deep dermis or subcutaneous fat layer, with or without adjacent muscle invasion. Lower extremity is the most common site, followed by the trunk unlike our experience. In our study upper extremity was the most frequent site followed by lower extremity. Histology better illustrates the secondary changes like hemorrhage and hemosiderin deposition.¹⁰ Vascular lesions cannot be categorised properly in cytology. They encompass a broad group of entities including vascular malformations, hyperplasias, hamartomas, dilation of local vessels and both benign and malignant vascular proliferations. Histopathology is the gold standard for

diagnosing these large group of diseases.¹¹

Benign epithelial and mesenchymal lesions far outnumbered (94.3%) their malignant counterparts (5.7%) in our study. Similar findings have been described by other authors.^{2,5} We encountered a single case of extra skeletal plasmacytoma similar to anjali et al in anterior chest wall.² It was confirmed with bone marrow aspiration study and urine protein electrophoresis. Adenocarcinomas were the most common epithelial metastatic malignancies in our study whereas squamous cell carcinomas were the largest group of primary cutaneous malignancies similar to other several authors.^{2,3} The most common cancers associated with cutaneous metastases are lung and colon in males and breast in females.^{12,13} Adenocarcinoma has been shown to be the most common histological variant of lung cancer.¹² Squamous cell carcinomas were

Table 4: Categorization and histology of benign lesions

Cytological diagnosis	Histological diagnosis	Benign	Malignant(1 ⁰ /Mets)	Disparity between cytology and histology diagnosis	Total (%)
Lipoma	Lipomas, atypical lipomas	560(56.1%)	02(0.2%)	1	562(56.2%)
Benign Spindle Cell Tumor	BFH*,desmoid tumor, Fibromatosis, DFSP‡, Nodular fasciitis	286(28.6%)	-	0	286(28.6%)
Appendageal Tumor	Pilomatricoma, Nodular hidradenoma, Cylindroma, Chondroid syringoma, Syringocystadenoma papilliferum, sebaceous adenoma, sebaceous carcinoma	51(5.1%)	2(0.2%)	2	53(5.31%)
Vascular Lesion	Capillary hemangioma, Atriovenous malformation, glomus tumor	53(5.31%)	-	0	53(5.31%)
Neural Tumor	Neurofibroma, schwannoma	16(1.6%)	-	1	16(1.6%)
GCT Tendon Sheath	GCT tendon sheath	28(2.8%)	-	0	28(2.8%)
Total		994(99.%)	4(4.8%)		998(100%)

*BFH: Benign Fibrous Histiocytoma ‡DFSP: Dermatofibrosarcoma protuberance

Table 5: Categorization of malignant lesions

Cytological diagnosis	Histological diagnosis	Number (%)	Site of Metastasis	Disparity between cytology and histology diagnosis	Total (%)
Adenocarcinoma	Adenocarcinoma lung	3	Trunk	0	11(32.3 %)
	small cell carcinoma lung	1	Trunk	0	
	Infiltrating carcinoma breast	4	Trunk, UE	0	
	carcinoma stomach,	1	Trunk	0	
SCC	carcinoma colon	2	Back	0	10(29.4%)
	Primary SCC	7	-	0	
	SCC Lung	2	Trunk,Back		
Malignant spindle cell tumor	granular cell tumor	1	Trunk	1	3(8.82%)
	Pleomorphic sarcoma	1	Trunk	0	
	LMS*	1	LE	0	
Metastatic malignant tumor deposit	Synovial sarcoma	1	LE	0	6(17.6%)
	Metastatic Germ Cell Tumor	2	Trunk	0	
Melanoma	Undifferentiated Tumor	2	Trunk	0	3(8.82%)
	BCC	2	-	2	
Plasmacytoma	Melanoma	3	-	1	1(2.94%)
	MM	1	Trunk	0	
Total		34(70.58%)			34(100%)

*LMS:Leiomyosarcoma

Table 6: Cytohistological and immunohistological correlation available

	Cytology diagnosis	Histology diagnosis	IHC
GCT tendon sheath	28(2.71%)	13(1.25%)	0
Adenocarcinoma	11(1.06%)	6(0.58 %)	2(0.19 %)
SCC	9(0.87%)	5(0.48 %)	0
Pleomorphic sarcoma	2(0.19 %)	2(0.19%)	0
Synovial sarcoma	1(0.09 %)	1(0.09%)	0
Metastatic germ cell tumor	1(0.09 %)	0	0
Undifferentiated tumor	3(0.39 %)	0	0
melanoma	3(0.39 %)	1(0.09%)	1(0.09 %)
Granular cell tumor	1(0.09 %)	0	0
plasmacytoma	1(0.09%)	1(0.09%)	1(0.09%)
Desmoids tumor	3(0.39 %)	2(0.19%)	1(0.09%)
BCC	2(0.19%)	2(0.19%)	0
Lipoma	562(54.4 %)	23(2.22%)	0
Appendageal tumor	53(5.1 %)	34(3.29 %)	0
Benign spindle cell tumor	283(27.4%)	35(3.39 %)	8(0.77 %)
Vascular lesion	53(5.13%)	10(0.96%)	0
Neural tumor	16(1.55%)	6(0.58%)	2(0.19%)
Total	1032(100%)	134(12.98 %)	14(1.35%)

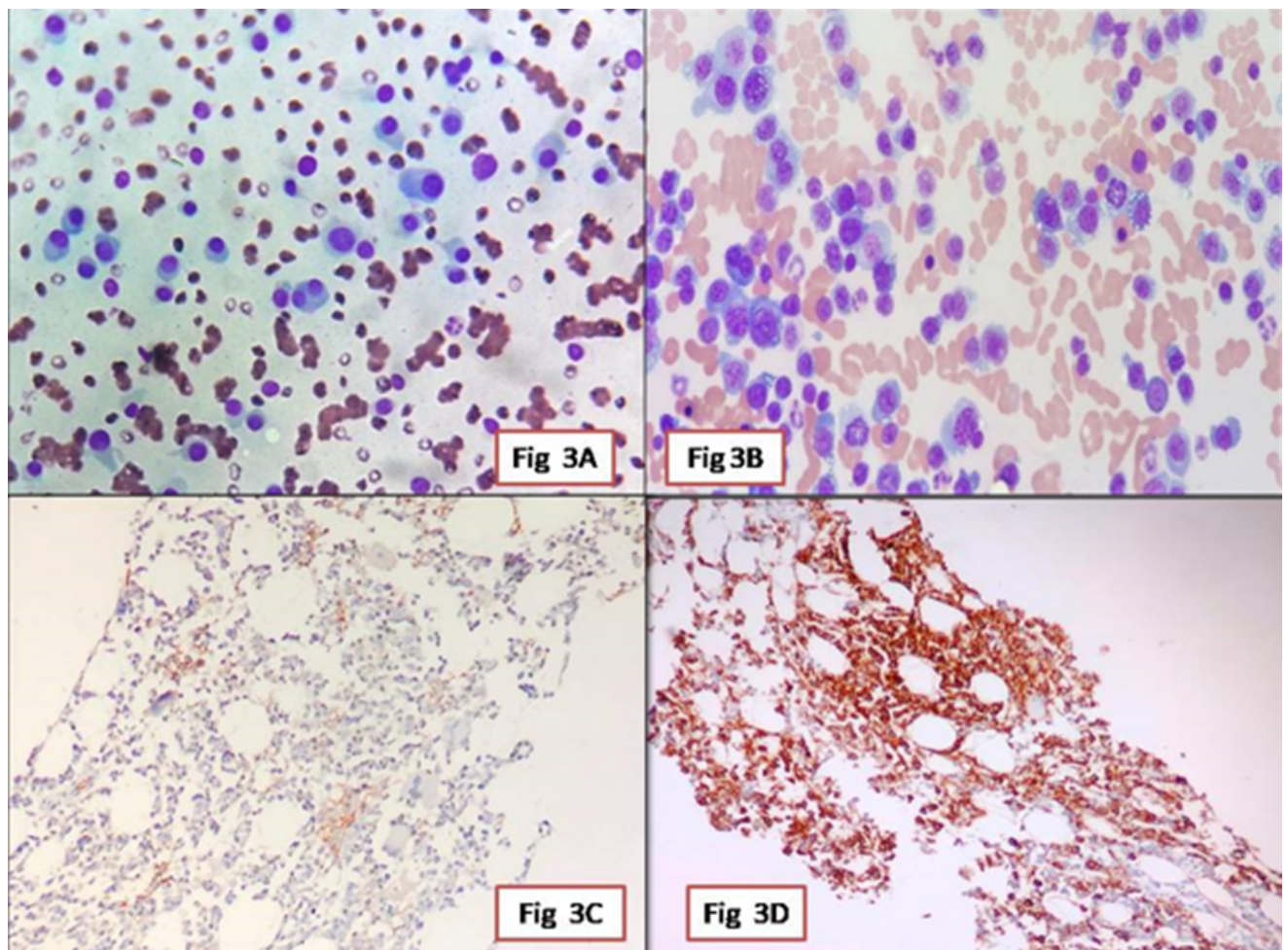


Fig. 3: **A:** Cytosmear show scattered mono and binucleated plasmacytoid cells, leishman stain, X100; **B:** Bone marrow aspiration: immature plasma cells (>90%), leishman stain, X100; **C:** Bone marrow biopsy: kappa negative in plasma cells, IHC, X100; **D:** Bone marrow biopsy : lambda positive in plasma cells, IHC, X100

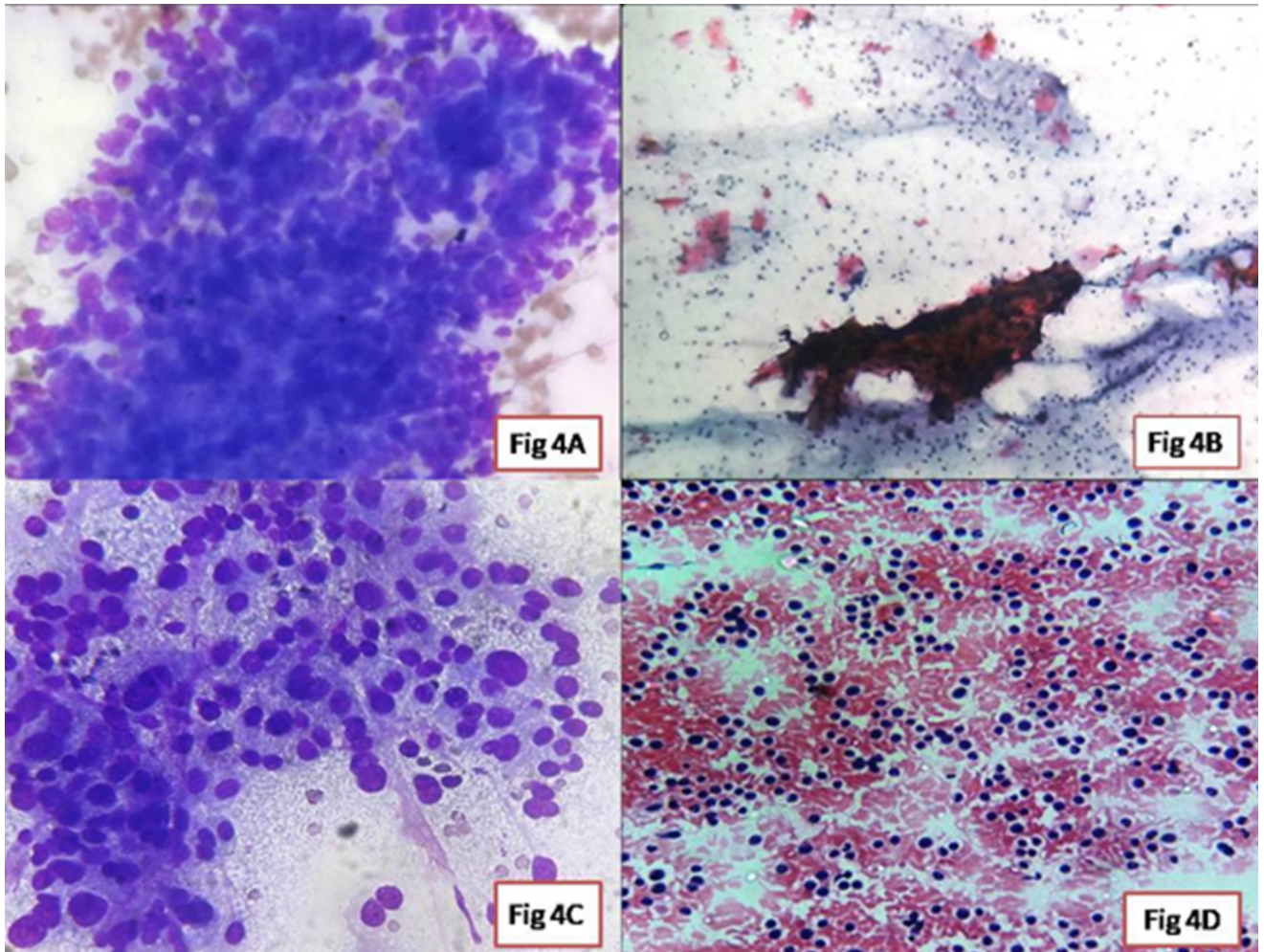


Fig. 4: **A:** Metastatic adenocarcinomatous deposit, Leishman stain,X100; **B:** Metastatic SCC deposit, papanicolaou stain,X100; **C:** Metastatic germ cell tumor deposit, Leishman stain,X100; **D:** Leukemia cutis, Leishman stain,X100

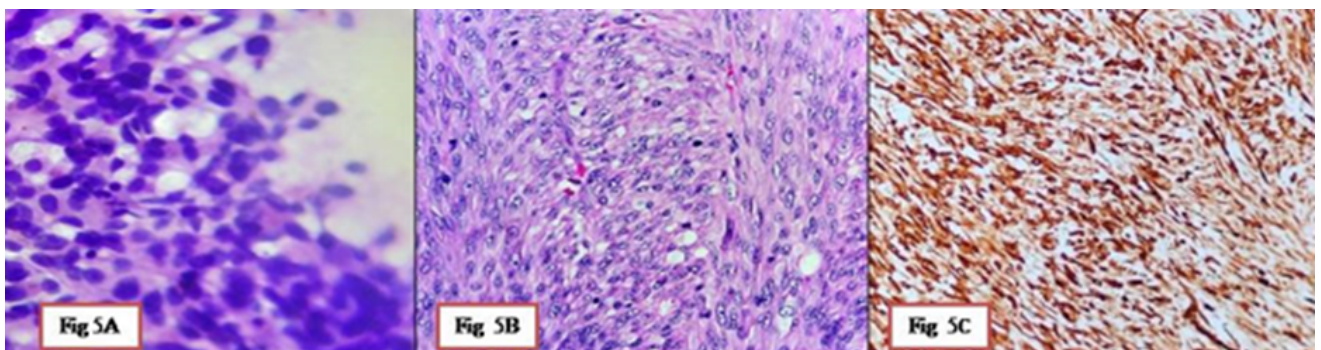


Fig. 5: **A:** Spindloid cells in clusters,leishman stain,X100; **B:** Leiomyoma: Long fascicles of smooth muscle cells intersecting at right angles, H& E,X100; **C:** Smooth muscle actin(SMA) positive,IHC,X100

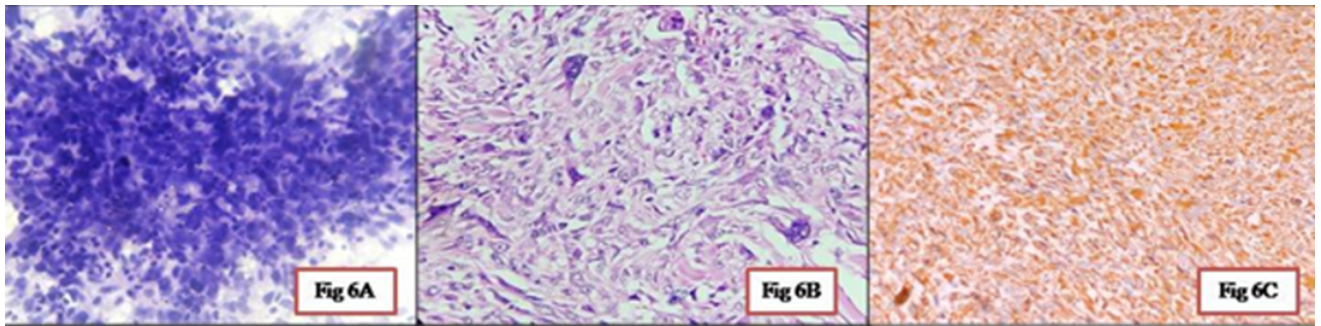


Fig. 6: **A:** Clusters of pleomorphic spindle cells, leishman stain,X100; **B:** Spindle cells in diffuse pattern with occasional large atypical bizarre cells in Pleomorphic sarcoma,H&E stain,X400; **C:** Vimentin cytoplasmic positive,IHC,X100

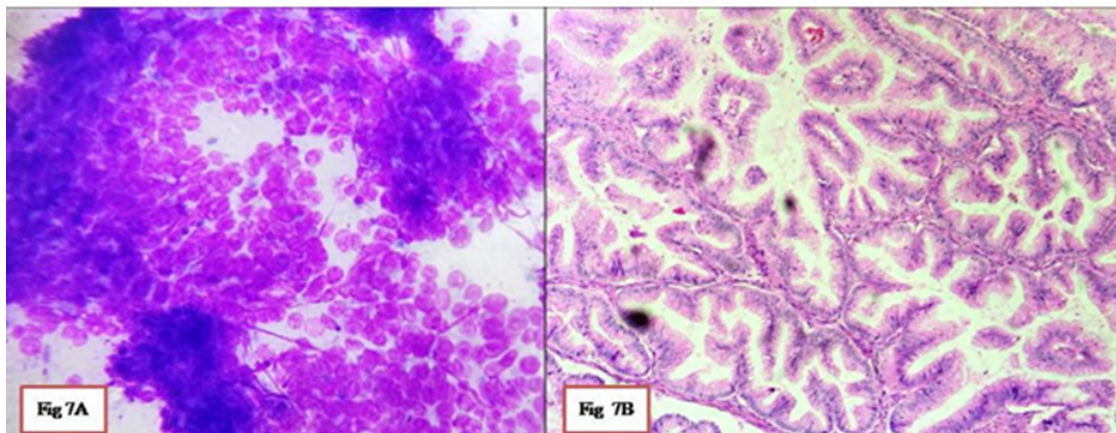


Fig. 7: **A:** Adenocarcinomatous deposit:Cluster of malignant epithelial cells, Leishman stain, X100; **B:** Well differentiated adenocarcinoma, H&E stain, X100

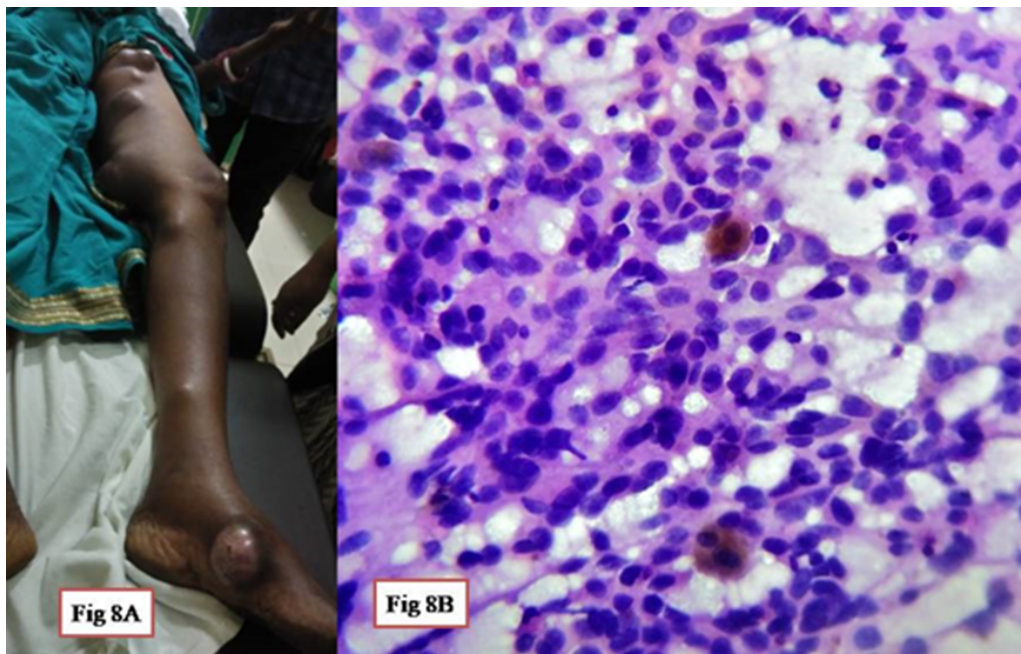


Fig. 8: **A:** Multiple large, soft nodules with blackish discoloration in left leg; **B:** Round to spindle cells in clusters with scattered melanin containing cells, Leishman stain,X100

located more in head and neck region in present study similar to anjali et al.² Metastatic cutaneous malignancies are indicative of widespread systemic malignancy with incidence of 0.7 to 10% heralding poor prognosis. Skin lesions may appear synchronous or metachronously to systemic malignancy.¹ Cutaneous metastases from small cell lung carcinoma (SCLC) are very rare with incidence of 0.3% to 0.8%.^{9,10} Our study had two such cases. Cutaneous metastases with a lung primary are relatively uncommon (24%) and point towards a poor prognosis. Our study had 11(32.3%) such cases.¹²

Malignant mesenchymal cutaneous malignancies were 8.82 % (3 cases) only in current study [Figure 6A-C]. Incidence of soft tissue tumours metastasising to skin is 1.8% [Figure 7A,B], [Figure 8A-D].¹⁴ In our study most common site of metastasis were chest wall. Common sites of metastases reported by different authors are chest, back, abdomen, head and neck.^{14–16} These are rare and present with lots of clinicopathological heterogeneity. They defy the common misconception that patients will be sick in appearance. Absence of various constitutional symptoms like fever, night sweats, pain, weight loss etc., should not deter the clinician's suspicion of malignancy in such cases.¹⁷ Clinically a slow growing, deep seated, soft to firm, mobile, large sized mass is indicative of benign lesion. On the other hand fast growing, large sized (>5 cm), firm to hard lesions are harbingers of malignancy. Clinical information like age of onset, site, presence of other symptoms, local and radiological examination and past history help in evaluation of such cases.¹⁸

Histology diagnoses were different in many cases compared to cytological interpretation in the study. This is due to 1) Overlapping morphology of different lesions in cytology, 2) small sample obtained in cytology procedure, hindering detail study unlike histology study, 3) application of broad terminologies and hesitation by cytopathologists to give more specific diagnosis in cytology in FNAC is considered a screening procedure only, 4) benign or premalignant skin lesions mimicking cutaneous malignancies like actinic keratosis, halo, dysplastic or spitz nevi, keratoacanthoma, pilar cysts, and seborrheic keratosis.¹

Out of 1032 cytologically diagnosed cases only in 134 cases further histopathological study and in mere 14 cases immunological study was undertaken. Lack of interest, financial issue are the factors behind this. Cytological diagnoses are many times very vague, e.g. benign spindle cell tumor, metastatic deposit etc. Histology not only helps in specific diagnosis of tumor, also in assessing grade, extent of invasion and prognosis of tumor. Further IHC study essential for targeted therapy. Hence biopsy and IHC study should be done in all cases. Six out of 12 adenocarcinoma cases were confirmed on histology in current study. One SCC was found to be granular cell tumor on histopathological study in current study.

Two metastatic deposit cases of high grade in cytology were rediagnosed as BCC again emphasising the fact that further histology and immunohistochemical studies needed for correct diagnosis in many cases. Another important aspect of diagnosing cutaneous tumors is that they may be associated with various syndromes. E.g. Neurofibroma in neurofibromatosis type 1, sebaceous tumors in Muir-Torre syndrome; Tricholemmomas, lipomas, angiomas in Cowden syndrome; Fibrofolliculomas and trichodiscomas in Birt-Hogg-Dubé syndrome etc.¹⁸

5. Limitations

Small sample size, lack of clinical, histological and IHC follow up in most of cases hampered our study from deriving useful significant conclusion in many cases.

6. Conclusion

Keeping in mind the dreadful consequences of many malignant cutaneous neoplasms they should be diagnosed earnestly with the help of radiology, histology, IHC and further molecular studies for effective management.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

8. Source of Funding

None.

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