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Inflammatory Myofibroblastic Tumors (IMT): Case Series with Emphasis on ALK Negative IMT

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Abstract:- IMT represents the neoplastic subset of the family of inflammatory pseudotumors, an umbrella term for spindle cell proliferations of uncertain histogenesis with a variable inflammatory component. It is important to recognise this entity for their unpredictable recurrent behaviour. We present a series of 7 cases of IMT involving different organs.Most of the patients were middle aged female. Oral cavity was the most frequent site followed by upper limb, lung and intestine. Recurrence was seen in patients with upper limb IMTs. IHC Alk was positive in only one case. Out of 7 cases, 4 cases had repeated negative biopsies. There is a long list of morphological differentials to exclude before diagnosing IMT. IHC can help to arrive at the diagnosis, but not without pitfalls and these cases highlight the need for clinicopathological and radiological correlation along with a high index of suspicion, and of course, the use of ancillary techniques such as IHC, FISH would adjunct to arrive at the accurate diagnosis.Alk negative IMT remains a masquerading entity about their diagnosis, pathology (? infective? neoplastic) and biological behaviour requiring more detailed genetic analysis and immunohistochemical studies for further classification.

Keywords:- *Myofibroblast, Inflammatory, Alk, Negative, Any, WHO,Intermediate*

I. INTRODUCTION

IMT represents the neoplastic subset of the family of inflammatory pseudotumors, an umbrella term for spindle cell proliferations of uncertain histogenesis with a variable inflammatory component.

The World Health Organization fascicle on soft tissues (2013) classifies it as a neoplasm of intermediate grade malignant potential with uncertain behaviour as local recurrence has been documented in approximately 25% of extrapulmonary cases and metastases may be seen in less than 2% cases. The propensity to recur depends on the anatomical site, multinodularity and resectability.

IMT encompasses a spectrum of myofibroblastic proliferation along with varying amount of inflammatory cell infiltrate, there by having three different variants 1)hypercellular or spindle cell variants, 2) hypocellularsclerosed variant and 3) hypervascularmyxoid variant. These patterns are often seen in combination within the same tumour, very rarely present as pure variants.

IMT affects all ages but is frequently a disease of children and young adults. Any sites can be involved with a predilection to lung, mesentery and omentum.[1] Among extrapulmonary IMT, 43% arise in the mesentery and omentum.[2] The upper aero-digestive tract comprises of 11% of all extra pulmonary cases with the larynx being most commonly affected site.[3]

On IHC, the myofibroblastic spindle cells show strong and diffuse positivity of vimentin, smooth muscle actin and occasional desmin, but lack other spindle cell tumour immunostainingmarkers like cytokeratin, S100, CD34 and vascular markers.

Approximately 50% of IMTs harbour a cytogenetic translocation that activates the anaplastic lymphoma kinase receptor tyrosine kinase gene located at 2p23 locus resulting in overexpression of ALK protein.Complete surgical excision is the treatment of choice because of its unpredictable clinical behaviour.There are now targeted therapy (crizotinib) available for ALK positive tumours and it is showing a promising results.

II. CASE SERIES

We could archieved 9 cases from the 10 years of our hospital database with a diagnosis of inflammatory myofibroblastic tumour, out of which 2 cases were not IHC proven. Most of the cases were commonly seen in adolescent and middle aged female. Oral cavity was the most frequent site followed by upper limb, lung and intestine. Recurrence was seen in patients with upper limb IMTs. IHC Alk was positive in only one case. Out of 7 cases, 5 cases had repeated negative biopsies. All patients had presented as nodular tumour in their respective site except one patientwho had presented as lung nodule was a known case of Alkpositive Anaplastic large cell lymphoma.All the patients were treated by surgery either by wide excision or by radical surgery except the lung tumour patient who was treated with 5 cycles of chemotherapy(vincristine and doxorubicin along with dexamethasone and cyclophosphomide).None of our patients had any systemic sign of inflammation by routine investigation . The details of case series were given below-

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N	Sex	Age	Site	Significant history	Size of the tumour	Incisional bx	IHC						treatment	Follow up
							sma	vim	S100	Cd34	other	alk		
1	M	48	lung	k/c/o ALCL	8.5x4cm	Repeated 2 times	+	+	-	-	EMA+(f), CD30+	+	5 cycles chemo	uneventful & alive
2	F	36	Left uper jaw	3 month duration	4x2.5cm	Repeat bx 2 times	+	+	-	-	CK-	ND	Partial alveolectomy	uneventful
3	M	02	Git	Ileocolic polyp	5x4cm	Not done	+	+	-	-	CD117-	-	Excision of polyp	Lost follow up
4	F	23	elbow	2 times recurrence within 2yrs	3x3cm	Repeated once	+	+	-	-	CK-	-	Only excision	uneventful
5	F	55	maxilla	2 month duration	6.5x5cm	Low grade spindle cell tumour probably IMT	+	+	-	-	Des+/- CK-	-	surgery	uneventful
6	F	16	forearm	3 times Recurrence within 3 years	5x5cm		+	+	-	-	CK-	ND	surgery	uneventful
7	F	50	LGBS	2 month duration	5x3cm	Repeated 3 times	+	+	-	-	ND	-	surgery	uneventful

Table 1:- Clinical Details of Cases

III. DISCUSSION

It has been almost 80 years since IMT was first observed in lungs by Bunn in 1939and was sonamed by Umiker*et al.* in 1954 because of its clinical and radiological behaviour that mimics a malignant process.[4] Recently, the concept of this lesion being reactive has been challenged based on the clinical demonstration of recurrences and metastasis and cytogenetic evidence of acquired clonal chromosomal abnormalities. Although the term IMT is used interchangeably with inflammatory pseudo tumour and by several other nomenclature due to presence of inflammatory cells, it should be discouraged to practice the same because of their clonal nature. Our case series showedthathead and neck region being the most common location which is supposed to be a rare site for IMT. In literature, larynx is found to be the most common site followed by oral cavity and facial bone with involvement of skull base in head and neck region.[5] Most of our patients were middle age & children with female preponderance, like in most of the other studies. IMT lung patient was associated with Anaplastic large cell lymphoma(ALCL). Studies have shown that a tentative analogy can be drawn between IMT and ALCL probably because of ALK family neoplasms.[6]

4 out of 7 cases were evaluated for Alk expression and only 1(lung case)showed positive results. Alkexpression is frequently seen in abdominal and pulmonary IMTs in the first decade of life and are associated with a higher frequency of recurrence.The IMTs without *ALK* abnormalities occurred in older, more frequently in females, and had fewer recurrences.[7] The exact characterization of Alk negative IMTs remains incomplete and controversial due to their vivid nomenclature and less number of reported cases. A few studies had mentioned about their tendency for distant metastasis while a few mentioning about their remission with antibiotics or steroids.[8,9] There are reports suggesting the presence of other subset of ALK-negative IMTs having ETV6–NTRK3 rearrangements as a possible oncogenic mechanism.[10]

Close differentials are- nodular fasciitis, fibrous histiocytoma,low grade myofibroblastic sarcoma, inflammatory fibrosarcoma, low grade neural lesions, fibromatosis. The bland histologic appearance of proliferating spindle cell in storiform pattern, no necrosis and pronounced plasma cell rich inflammatory cells in sclerosed or myxoidbackground is characteristic. With IHC support of myofibroblastic phenotype will help to arrive at the diagnosis.

It is quite common for patients with IMT to undergo multiple biopsy procedures to establish a diagnosis because of their hypocellular and myxoid areas. On biopsy evaluation, IMT appears to be a diagnosis of exclusion. The diagnostic accuracy of incisional biopsy in hypocellular and vascular variant can be improved by correlation of morphology with clinicoradiological findings.

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IV. CONCLUSION

We present a few examples of IMT involving various organs requiring a high index of suspicion, clinicopathological correlation and the use of ancillary techniques such as IHC, FISH for accurate diagnosis.Alk negative IMT remains a masquerading entity about their diagnosis, pathology (? infective? neoplastic) and biological behaviour. It is possible that ALK negative IMTs will be reclassified in the future, based on more detailed genetic analysis and immunohistochemical studies of the lesion.

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➢ *List of Abbreviations-*

- IMT-Inflammatory myofibroblastic tumour
- LGBS- Lower gingivo buccal sulcus
- ND- Not done
- ALCL- Anaplastic large cell lymphoma
- ALK- Anaplastic lymphoma kinase

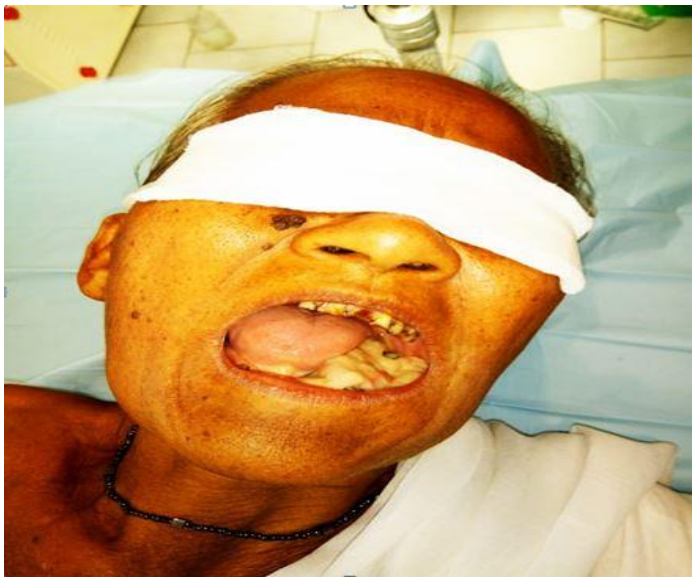

Fig 1:- 50 year Female with LGBS Swelling

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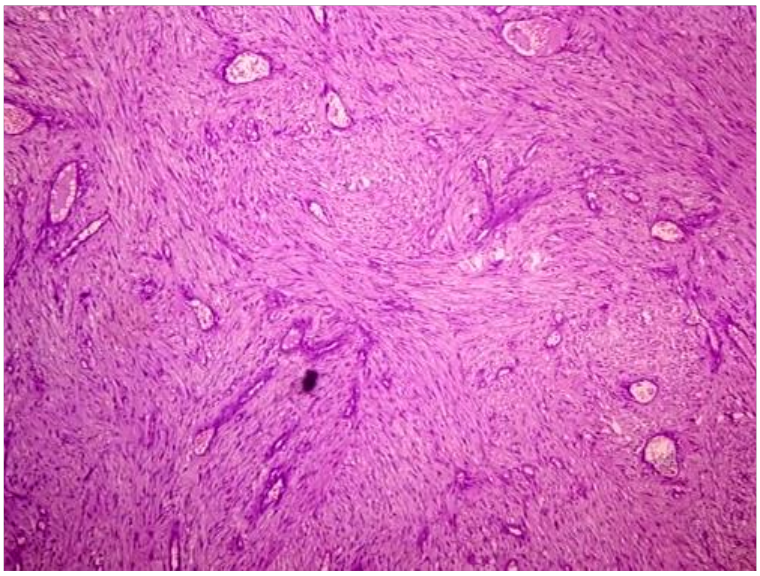

Fig 2:- H&E, 100X, Bland Spindle Cells in Fascicles

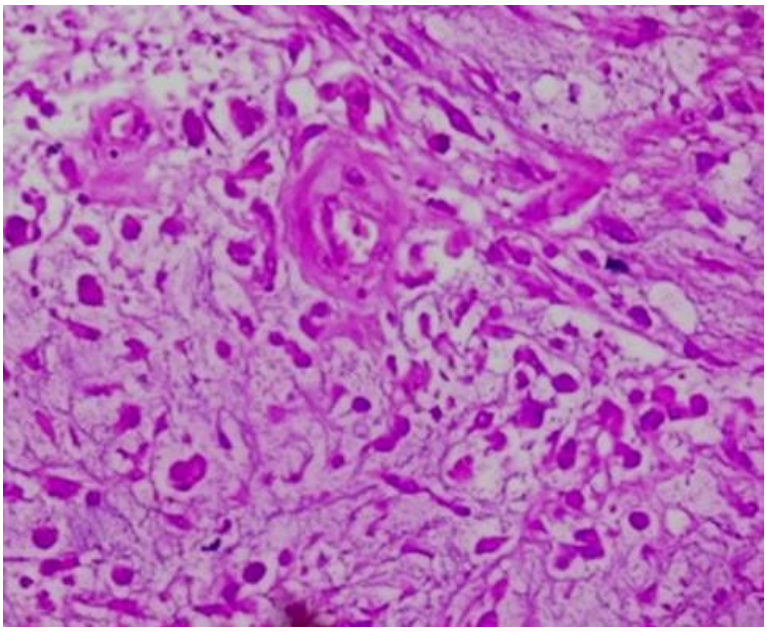

Fig 3:- H&E, 400X, Stellate Cells, Plasma Cells in Myxoid Background

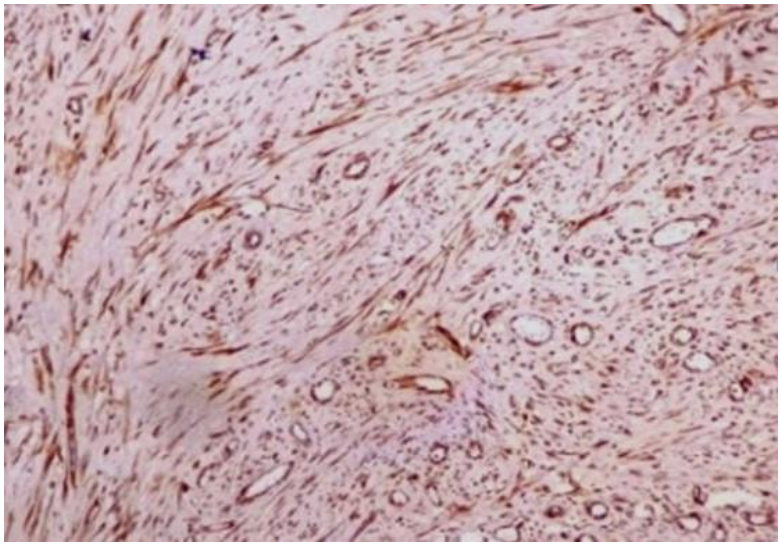

Fig 4:- IHC, 100X, Diffuse Vimentin Positivity

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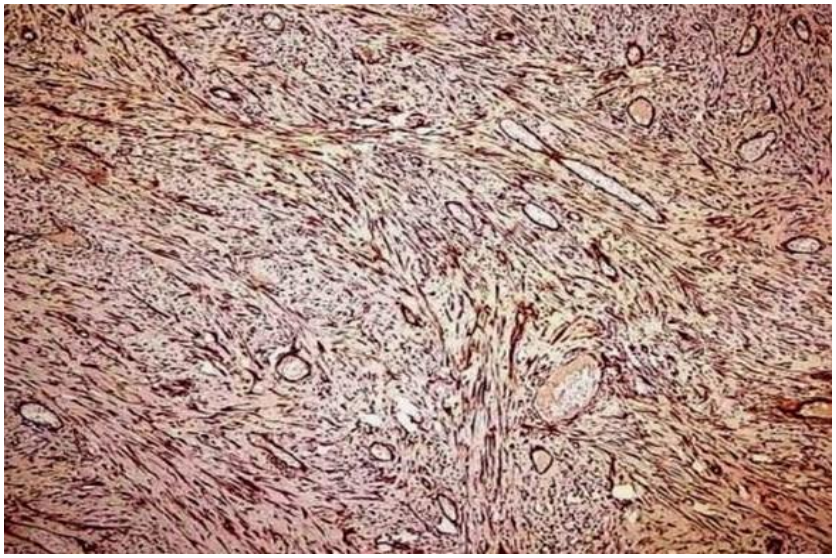

Fig 5:- IHC, 100X, SMA Positivity in Spindle Cells

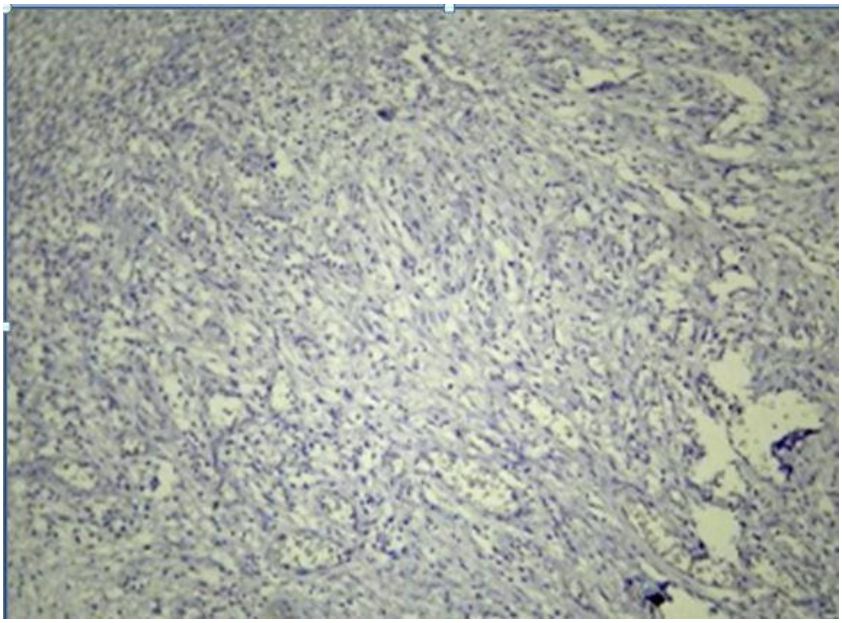

Fig 6:- IHC, 100X, Alk Negative