Original Article

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Pathology Section

Unravelling the Enigma of Inflammatory Myofibroblastic Tumours: A Cross-sectional Study from a Regional Cancer Centre, Karnataka, India

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ABSTRACT

Introduction: Inflammatory Myofibroblastic Tumour (IMT) is an unusual neoplasm with intermediate malignant potential, which rarely metastasises. IMT occurs in various anatomical sites, and the initial descriptions were primarily centered on its manifestation in the lungs. Although the age range is broad, IMT is most common in the first three decades of life, with a slight female predominance. Recent data and Anaplastic Lymphoma Kinase (ALK) gene aberrations confirm a neoplastic process for these lesions.

Aim: To study the clinicopathological features of IMTs in a regional cancer centre in South India.

Materials and Methods: A cross-sectional study included 17 cases of IMT over six years, from May 2014 to May 2020, at Memorial Kidwai Memorial Institute of Oncology (KMIO), Bengaluru, Karnataka, India. The clinicopathologic and immunophenotypic features were analysed on needle biopsies and resected specimens. Correlation between the expression of ALK-1 and histological patterns, mimickers, metastasis, and prognosis were described. Results were analysed using Microsoft Excel 2019 and Medcalc calculator.

Results: Seventeen cases of IMTs were included in this study, out of which two were in the lung, and the rest were extrapulmonary. Sixteen cases were unifocal on presentation; however, one IMT of extremity showed evidence of secondaries on bone scan. The mean age at presentation was 33.47 years, and the male-to-female ratio was 1:1.12. Among the seventeen cases, sites are as follows: one each in the retroperitoneum, liver, soft-tissue (extremity), two each in the breast, lung, female genital tract, urinary bladder, and three each in the head and neck region (maxilla, trachea, and alveolus) and mesentery. Microscopically, IMTs showed various histological patterns. Immunostaining for ALK-1 was positive in seven out of seventeen cases, and the rest were diagnosed by excluding closer mimickers.

Conclusion: The present study provides crucial insights into the clinicopathological features of IMTs. Immunohistochemistry (IHC) is an essential diagnostic tool that helps accurately differentiate IMT from its mimickers by identifying ALK protein expression. This distinction is essential for guiding targeted therapy in recurrent or metastatic cases.

Keywords: Diagnosis immunohistochemistry, Metastatic, Neoplasms

INTRODUCTION

WHO defines IMT as a distinct neoplasm composed of myofibroblastic, fibroblastic spindle cells, and inflammatory cell infiltrates [1]. This is more commonly seen in the first three decades, with a slight female predominance. Original descriptions of IMT were focused on lungs [2,3]. According to the WHO, the most commonly reported sites include mesentery, omentum, retroperitoneum, lung, mediastinum, and head and neck [1]. Unusual locations include somatic soft-tissue, gastrointestinal tract, uterus, bladder, pancreas, and CNS [1].

Microscopically, they comprise of spindled to plump myofibroblasts in an oedematous myxoid background with lymphoplasmacytic infiltrate. There are three basic histological patterns: myxoid, hypercellular, hypocellular, and a rare subtype with epithelioid morphology [1,4,5].

IHC for ALK shows variable expression, which also depends on its fusion partner [6,7]. ALK positivity is seen in 40-60% of the IMT cases [1]. Because of its ambiguous clinical presentation, it must be differentiated from other closer mimickers like infectious, granulomatous, autoimmune, and malignant lesions based on histopathologic findings and immunohistochemical analysis [8]. A rare variant of IMT with epitheloid morphology has a poor prognosis with rapid development of local recurrence. It has been recognised as a variant of IMT with RANBP2-ALK gene rearrangement [1,4]. ALK-1 expression is also prognostically important.

IMT is a diagnosis of exclusion and must be distinguished from other closer mimics. ALK protein expression by IHC and/or gene rearrangement favour the diagnosis of IMT over another differential diagnosis in challenging cases, although ALK expression can be variable. It also aids in selecting targeted therapy in recurrent or metastatic disease. ALK expression is also correlated with recurrence and metastasis. In the present study, the authors aimed to analyse the clinicopathological and immunophenotypical features of IMT.

MATERIALS AND METHODS

A six-year cross-sectional study was conducted from May 2014 to May 2020 in the Department of Pathology at Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. Since the study was retrospective and did not involve any intervention, an exemption from the ethical committee was obtained. All newly clinically and radiologically investigated cases of IMT were included in the study, and recurrent disease at presentation was excluded.

The study comprised 17 cases of IMT, including 13 institutional and four review cases from elsewhere. Clinical details were obtained from hospital records. The clinicopathologic and immunophenotypic features were analysed on needle biopsies (n=7) and resected specimens (n=10). The study evaluated the age and gender of patients, the affected sites, and the gross findings. Various histological patterns were observed, and ALK-1 expression was correlated with histological patterns, metastasis, and recurrence.

Haematoxylin and Eosin (H&E) stained sections were examined and classified into three main histological patterns and a rare epithelioid

subtype based on morphological criteria described in the WHO classification of tumours of soft tissue and bone. The patterns observed were myxoid, hypercellular, hypocellular, and the rare epithelioid subtype, which is considered aggressive.

IHC was performed to rule out other closer mimickers, such as granulation tissue, nodular fasciitis, dermatofibroma, inflammatory fibroid polyp, fibromatosis, leiomyoma, gastrointestinal stromal tumour, leiomyosarcoma, Ewing's sarcoma, rhabdomyosarcoma, and melanoma. Several markers were used, including Pancytokeratin (PanCK), Epithelial Membrane Antigen (EMA), CD34, CD68, Smooth Muscle Actin (SMA), S-100, Vimentin, Desmin, ALK-1, Myogenin, Myo D1, CD117, beta-catenin, H Caldesmon, MIC 2/CD99, melan A, and Ki67. The clone used for ALK IHC was SP144 (Rabbit monoclonal). The stain was considered positive when the tumour cells expressed specific cytoplasmic and/or nuclear membrane staining for the antibody used. Slides observed were assigned a score of 0 (no staining - negative), 1 (<10% of neoplastic cells staining - weak positive), 2 (10%-50% of neoplastic cells staining - moderate positive), or 3 (>50% of neoplastic cells staining - strong positive).

The study results were analysed using Microsoft Excel 2019.

RESULTS

Clinical Characteristics

Out of the 17 cases of IMTs identified in the present study, two were in the lung, while the rest were extrapulmonary, and the cases were reviewed. The mean age at presentation was 33.47 years. The study included eight male (n=8) and nine female patients (n=9), resulting in a male-to-female ratio of 1:1.12. Among the seventeen cases, the sites were as follows: one each in the retroperitoneum (n=1), liver (n=1), and soft tissue (extremity) (n=1); two each in the breast (n=2), lung (n=2), female genital tract (n=2), and urinary bladder (n=2); and three each in the head and neck region (maxilla, trachea, and alveolus) (n=3) and mesentery (n=3) [Table/Fig-1]. Sixteen cases were unifocal on presentation; however, one IMT of the extremity showed evidence of secondary involvement on a bone scan during follow-up.

Uncommon Findings

Case number 13 involved a 65-year-old male patient with left ankle swelling. An X-ray revealed an ill-defined soft-tissue density lesion around the ankle joint, extending into the plantar and dorsal aspects of the foot with erosion of the tarsal bones [Table/Fig-2a]. A follow-up Computed Tomography (CT) scan of the abdomen showed hepatic metastasis, and a bone scan revealed abnormally increased radiotracer concentration at multiple sites (left parietal bone, right temporal bone, and in the left iliac bone close to the sacroiliac joint), suggestive of numerous skeletal secondaries [Table/Fig-2b]. The patient underwent left below-knee amputation, which was followed by a histological examination suggesting epithelioid IMT.

In case number 11, a 50-year-old female patient had an IMT in the trachea. She presented with slightly higher Ig M levels, i.e., 262.2 mg/dL (Normal range for adults: 40-230 mg/dL), and a possible M spike in the beta region; however, her bone marrow examination ruled out plasma cell neoplasm.

Gross findings: Most tumours were nodular/multinodular masses with a tan, fleshy, or myxoid appearance. The resected specimens ranged in size from 2 to 15 cm and exhibited nodular, well-circumscribed to polypoidal appearances. The cut surface showed grey-white to grey-brown areas, which were firm in consistency. Variable areas of haemorrhage, necrosis, and calcification were observed. [Table/Fig-2c] shows a gross picture of a case of bladder IMT (case number 3 in a 10-year-old male child), having a mucoid and glistening appearance.

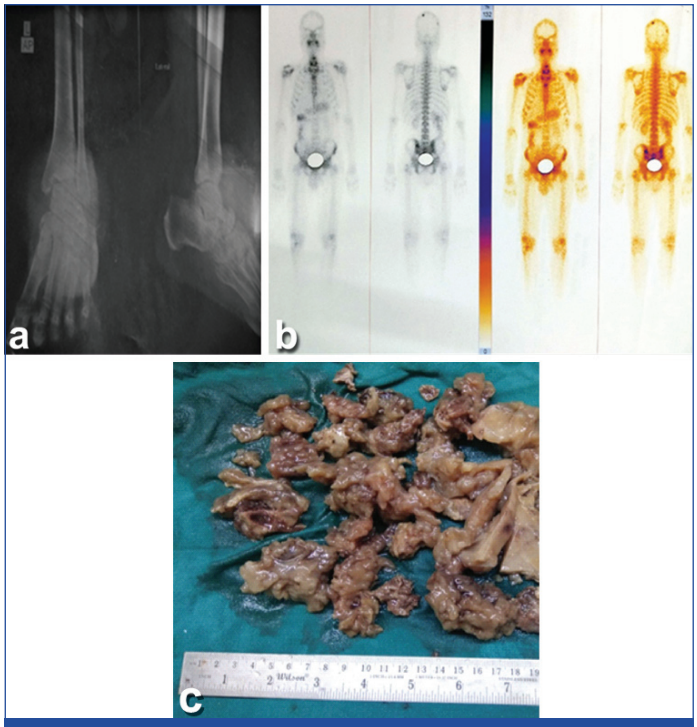
Treatment and follow-up data: The primary treatment modality was surgical excision with negative margins. All cases, except two, underwent surgical excision. In cases where the location was inoperable, or when only a biopsy was done, or in localised lesions with R1 resection (microscopic positive resection margin), vinblastine and methotrexate were administered along with other chemotherapy regimens. If the patient presented with a positive ALK status in recurrent or metastatic disease, crizotinib was administered.

Out of 17 cases, 13 were followed-up, of which five patients showed disease-free survival, two were alive with evidence of local recurrence on follow-up, and four were alive with no evidence of disease on the last follow-up. One patient remained symptomatic, and another died of the disease. One of the recurrent cases showed metastasis and succumbed to the disease.

Histological characteristics and immunohistochemical staining: Microscopically, all tumours were composed of fascicles of spindled myofibroblasts intermingled with lymphoplasmacytic infiltrate and were categorised as follows according to the WHO. [Table/Fig-3a-e] shows the various histological patterns observed in the current

Case number	Age (years)	Sex	Site	Specimen type	Histopathological subtype	ALK 1	SMA	Metastasis	Recurrence
1.	9	M	Lung	Biopsy	C	+	-	-	-
2.	10	M	Mesentery of the small intestine	Resection	B	+	+	-	-
3.	10	M	Bladder	Biopsy	A	+	+	-	-
4.	11	M	Mesentery of the small intestine	Resection	B	+	+	-	-
5.	12	M	Maxilla	Resection	B	-	+	-	-
6.	23	F	Ovary	Resection	C	-	+	-	-
7.	30	F	Breast	Resection	B	-	+	-	-
8.	33	F	Breast	Resection	B	-	+	-	-
9.	40	M	Retroperitoneum	Biopsy	A	+	+	-	-
10.	43	F	Bladder	Resection	A	-	+	-	-
11.	50	F	Trachea	Resection	B	-	+	-	Yes
12.	60	F	Cervix	Biopsy	C	-	+	-	-
13.	65	F	Ankle (Soft-tissue- Extremity)	Resection	D	-	-	Yes	Yes
14.	74	F	Alveolus	Resection	B	-	+	-	-
15.	16	M	Mesentery-Colon	Biopsy	A	+	+	-	-
16.	35	F	Lung	Biopsy	D	-	+	-	-
17.	48	M	Liver	Biopsy	B	+	-	-	-

[Table/Fig-1]: Clinicopathological characteristics.
*M: Male; F: Female; A: Myxoid; B: Hypercellular with inflammatory cell infiltrate; C: Hypocellular; D: Epithelioid



[Table/Fig-2]: a) X-ray, AP, and lateral view of the left ankle with the foot showed an ill-defined soft-tissue density lesion; b) Bone scan image revealed an abnormally increased radiotracer concentration at multiple sites; c) Gross picture of bladder IMT showing mucoid and glistening areas.

study: spindled/plump myofibroblasts in a myxoid background (n=4), hypercellular pattern with fascicles of spindle cells with distinct inflammatory cell infiltrate (n=8), hypocellular fibrous pattern (n=3), and epithelioid morphology (Epithelioid Inflammatory Myofibroblastic Sarcoma (EIMS)) (n=2). Fifteen cases showed classical morphology, whereas two had EIMS [Table/Fig-3a-e].

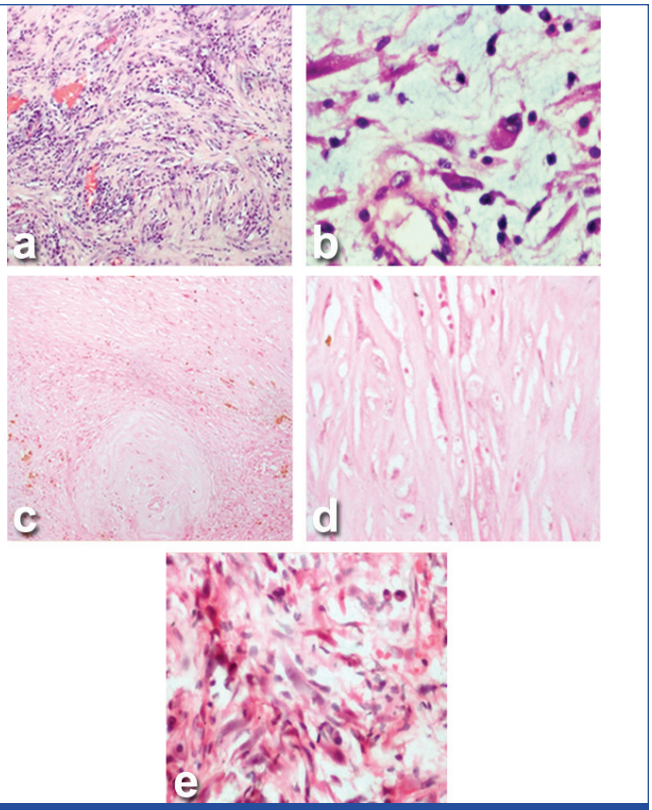
Immunohistochemistry (IHC): Immunostaining for ALK-1 was positive in 7 out of 17 cases [Table/Fig-4a,b]. There was variable expression for SMA (n=14, 82.35%), vimentin (n=6, 35.29%), desmin (n=5, 29.41%), EMA (n=1, 5.88%), and weak focal CD 68 immunoreactivity (n=4, 23.52%) [Table/Fig-4a-e]. Cells were negative for Myo D 1, myogenin, CD117, CD34, beta-catenin, H caldesmon, MIC 2, and melan A, which helped rule out other benign and malignant spindle cell neoplasms that mimic IMT.

DISCUSSION

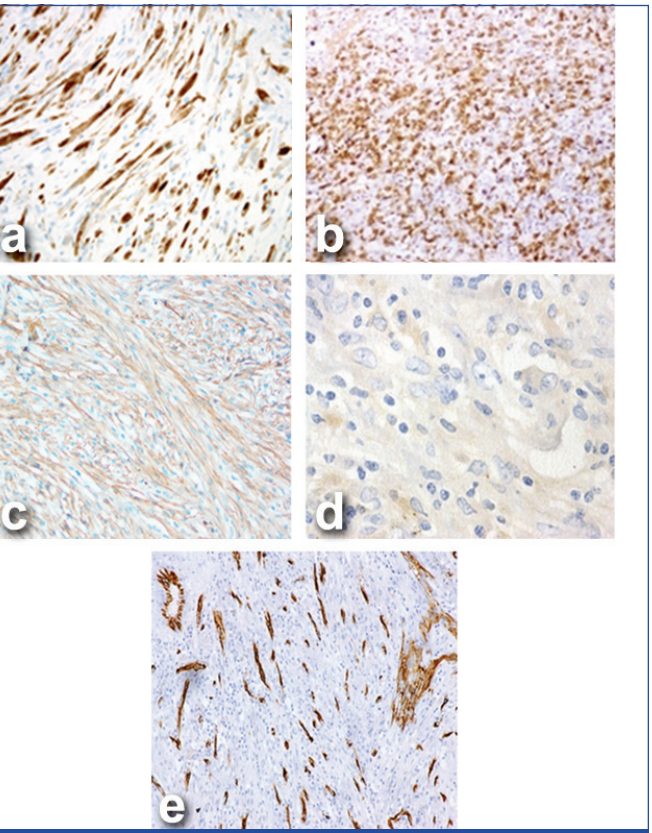
According to the WHO, IMT is a heterogeneous neoplasm classified under the intermediate and rarely metastasising group. Brunn first described IMT in 1939 [5], and it was named by Umiker WO and Iverson L in 1954 [3]. According to KMIO statistics, IMT constituted 10% of fibroblastic/myofibroblastic tumours and 2.5% of soft-tissue tumours during the study period (departmental statistics).

IMT primarily affects children and young adults, although the age range extends throughout adulthood, and in our present study, 35.29% of children and young adults were involved. According to the literature, IMT mainly affects the lung [3]; however, in the present study, pulmonary IMT constituted only about 11.76%, and we had a higher number (88.24%) of extrapulmonary cases. According to Wang Z et al., the most common site was the abdominopelvic region (73.9%), followed by other locations; their observations were similar to the present study, wherein IMTs in the abdominopelvic region constituted about 52.9% [6]. Extrapulmonary sites are rarely reported in the literature [9], and even rarer are sites like soft tissues of the extremities, bones, and joints [10-19]. Only a few case reports on soft-tissue IMT [16,17] exist. The present study included a rare case of soft-tissue IMT (ankle) with recurrences and metastasis, which had EIMS.

The WHO classification of soft-tissue and bone tumours categorises IMT into three basic histologic patterns and a rare subtype with



[Table/Fig-3]: a) Microscopy-H&E X100 shows fascicles of spindled myofibroblasts interspersed with moderate chronic inflammatory cell infiltrate, comprising of lymphocytes, plasma cells, and blood vessels- Hypercellular pattern; b) H&E X400 shows spindled/plump (Ganglion-like) myofibroblasts in a myxoid background admixed with lymphocytes, plasma cells, and blood vessels- Myxoid pattern; c) H&E X100 shows a hypocellular and fibrous pattern, composed of a few myofibroblasts and capillaries set in a fibrous background and blood vessels; d) H&E X400 shows myofibroblasts having vesicular chromatin, small prominent nucleoli, and a moderate amount of eosinophilic cytoplasm; e) H&E X400 shows plump to spindly epithelioid cells with vesicular chromatin, prominent nucleoli, and moderate to abundant amount of amphophilic/eosinophilic cytoplasm, displaying mild pleomorphism, admixed with few lymphocytes and neutrophils against a myxoid stroma-EIMS.



[Table/Fig-4]: a) IHC X100 shows the nuclear expression of ALK; b) IHC X100 shows nuclear and cytoplasmic ALK positivity; c) IHC X100 shows cytoplasmic expression of SMA; d) IHC X100 shows weak cytoplasmic expression of Pan Cytokeratin; e) IHC X 100, CD34 shows membranous expression in the endothelial cells of blood vessels.

epithelioid morphology [1]. The patterns are as follows: myxoid, hypercellular, and hypocellular. Essential criteria include spindled to plump myofibroblasts, mixed inflammatory cell infiltrate, and variable fibrous-myxoid stroma. It is important to differentiate them from other similar conditions such as Nodular fasciitis, fibromatosis, inflammatory fibroid polyps, and granulation tissue, with the help of IHC.

In the present study, extrapulmonary cases outnumbered pulmonary cases, and ALK-1 expression was noted in 41.2% (n=7) of cases. Recurrence was noted in two cases (11.7%) and metastasis in one case (5.9%), both of which showed ALK-1 negativity. In a similar study of 18 cases by Telugu RB et al., pulmonary IMTs outnumbered other sites, ALK-1 expression was noted in 55.6% of cases, and recurrence was noted in 30% of ALK-1 positive cases and 37.5% of ALK-1 negative cases. Metastasis was noted only in the ALK-1 positive group [7]. There was no statistically significant correlation between ALK-1 expression and tumour recurrence or metastasis.

Jiang YH et al., in their retrospective study of 15 cases, found a significant correlation between ALK-1 positivity and lower rates of recurrence and metastasis in IMTs [20]. Recurrence was noted in 25% and 63.6% of ALK-1 positive and negative IMTs, respectively. Metastasis was noted only in the ALK-1 negative group [Table/Fig-5]. This explains the variability in the site of occurrence and clinical behaviour of IMT in association with ALK.

Study	Pulmonary cases	Extrapulmonary cases	ALK expression	Recurrence	Metastasis
Present study (n=17)	11.76% (n=2)	88.24% (n=15)	41.17% (n=7)	Associated with ALK negativity*	Associated with ALK negativity*
Telugu RB et al., (n=18) [7]	27.78% (n=6)	72.22% (n=12)	55.6% (n=10)	More among ALK-negative*	Associated with ALK positivity*
Jiang YH et al., (n=15) [20]	26.66% (n=4)	73.34% (n=11)	26.66% (n=4)	Significant association with ALK negativity	Significant association with ALK negativity
Chougule A et al., (n=7) [23]	71.43 (n=5)	28.57 (n=02)	57.14 (n=4)	Association with ALK negativity	NA

[Table/Fig-5]: Comparison of site, ALK expression with recurrence and metastasis in related studies.
*Statistically not significant

IMTs show variable staining for SMA, Muscle-Specific Actin (MSA), and Desmin. These tumours were considered a neoplasm after the discovery of clonal rearrangement of the ALK gene. Approximately 50-60% harbor clonal rearrangements at 2p23, and this gene has a variety of fusion partners, including TPM3, TPM4, CLTC, CARS, ATIC, SEC31L1, AND RANBP2 [1]. A previous study by Chaudhary P showed that ALK gene rearrangement was higher in younger individuals compared to adults, similar to the present study where ALK positivity was observed in young male individuals aged 9-11 years (Case-1-4,15) [21]. However, we observed that ALK expression was predominantly seen in males. An 11-year retrospective study by Wang Z et al., on 23 cases of IMT revealed that ALK-1 was negative in 11 out of 13 cases, reflecting the variable expression of ALK-1 [6]. According to Mariño-Enríquez A et al., ALK-1 positivity was demonstrated in IMT with epithelioid morphology, but in the present study, ALK-1 was negative in cases with epithelioid morphology [22]. However, FISH could not be done due to financial constraints. While recent literature lacks studies directly comparing ALK expression and recurrence risk, a study of seven cases comparing morphological aspects of IMT and IgG4-related disease included four ALK-positive cases. Interestingly, among the remaining three ALK-negative cases, two experienced recurrence, and none had metastasis. This study indirectly suggests that there may not be a significant association between ALK positivity and recurrence, which is in line with other similar studies and our own findings [23].

The localisation of ALK-1 within the cell is determined by its fusion partner [1]. Diffuse cytoplasmic staining is observed with TPM3, TPM4, CARS, ATIC, and SEC31L1, and nuclear staining with RANBP2. Granular cytoplasmic staining is observed with the fusion partner CLTC [1,2]. RANBP2-ALK fusion, which shows a distinctive ALK nuclear membrane immunoreactivity pattern, behaves aggressively [24]. Evidence of kinase fusion supports targeted therapy with tyrosine kinase inhibitors, including crizotinib [25,26].

Interestingly, ETV6-NTRK3 fusion is reported in ALK-negative IMTs [2]. Intra-abdominal IMTs are associated with recurrence [6]. According to the literature, 25% of extrapulmonary IMTs recur, and metastasis is rare, at 2% [1]. In the present study, recurrence and metastasis were observed in a case of soft-tissue IMT of the extremity. IMTs with epithelioid morphology behave aggressively [1,26]. According to the WHO, ALK-negative IMTs have a higher likelihood of metastasis, similar to the findings in the present study. These ambiguous tumours of unknown etiology can occur anywhere in the body, including rare locations such as intracranial, orbital, and spinal regions, and hence extensive work-up and IHC support making the final diagnosis [26]. ALK expression helps confirm a case of IMT and has a role in prognosis and survival. IMTs exhibit heterogeneous clinical presentations, varied molecular expressions, and diverse outcomes, underscoring the enigmatic nature of these tumours. By unraveling the molecular mechanisms that drive these tumours, more effective treatment can be provided, which further improves diagnostic accuracy.

Limitation(s)

The present study was limited by the smaller number of cases, and FISH for ALK gene rearrangement was not performed due to financial constraints.

CONCLUSION(S)

IMT is a diagnosis of exclusion and must be distinguished from other closer mimics. ALK protein expression by IHC and/or gene rearrangement by FISH favours the diagnosis of IMT over other mimickers in challenging cases. While the study sheds light on the diagnostic utility of ALK protein expression in distinguishing IMTs, further investigations are warranted to explore the underlying molecular mechanisms driving the neoplastic process. Additionally, prospective studies could assess the efficacy of targeted therapies based on ALK status, paving the way for personalised treatment strategies in the management of IMTs. Collaborative efforts and larger cohorts may provide deeper insights into the prognostic significance of specific histological patterns and guide clinical decision-making.

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