Anaplastic lymphoma kinase (ALK 1) staining and molecular analysis in inflammatory myofibroblastic tumours of the bladder: a preliminary clinicopathological study of nine cases and review of the literature

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Inflammatory myofibroblastic tumours (IMFT) may arise at any anatomical site, including lung, soft tissues, retroperitoneum and bladder. Although morphologically similar, these lesions encompass a spectrum of entities with differing aetiology, ranging from reactive/regenerative proliferations to low-grade neoplasms with a risk of local recurrence, but no significant metastatic potential. Vesical IMFT usually presents as a polypoid mass with a pale firm cut surface and can be of considerable size, mimicking a malignant tumour clinically and radiologically. Its good outcome, however, warrants conservative surgical excision, emphasising the importance of identification and distinction from malignant tumours of the bladder that may require more radical surgery and/or adjuvant therapy. We conducted a preliminary retrospective, comparative immunocytochemical study of 20 bladder tumours, including nine IMFTs, five spindle cell (sarcomatoid) carcinomas, two rhabdomyosarcomas, two leiomyosarcomas and two neurofibromas. The results confirmed IMFT positivity for smooth muscle actin, desmin and cytokeratin in 78–89% cases, resulting in potential confusion with sarcomatoid carcinoma or leiomyosarcoma. In contrast, cytoplasmic anaplastic lymphoma kinase (ALK 1) staining was present in eight IMFT (89%), but was not seen in any other lesion examined. The ALK 1 staining was confirmed by fluorescence *in situ* hybridisation, with translocation of the ALK gene present in 15–60% tumour cells in four of six IMFT examined, but not in four cases of sarcomatoid carcinoma or three of leiomyosarcoma. In conclusion, ALK 1 staining may be of value in the distinction of vesical IMFT from morphologically similar entities, and often reflects ALK gene translocations in these lesions.

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Attributed initially to the lung,¹ inflammatory myofibroblastic tumours (IMFT) are now known to arise in a wide variety of body sites, including the abdominal cavity, retroperitoneum, pelvis and bladder.^{2–5} In the early literature, these lesions were classified into separate groups based on their anatomical site and postulated aetiology, using terms such as ‘inflammatory pseudotumour’, ‘in-

flammatory fibromyxoid tumour’, ‘postoperative spindle cell nodule’ and ‘plasma cell granuloma’.^{6–8} More recently, IMFT has been widely accepted as the terminology for a subset of these lesions that are thought to be neoplastic in nature, while other cases thought to be infective, inflammatory or reactive in origin are called ‘pseudotumours’.⁹

Studies of IMFT at a variety of anatomical sites have shown that these tumours present most frequently in children and young adults (mean age 9–10 years), with rare cases in middle age.^{10,11} They arise slightly more commonly in females (M:F=3:4) and may reach up to 17 cm in size (mean 6 cm). Clinical presentation is usually as a mass lesion, with symptoms of pain, fever and

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weight loss and haematological findings of anaemia, thrombocytosis, increased erythrocyte sedimentation rate (ESR) and raised gamma globulins.¹²

Three main microscopic patterns are recognised in IMFT: (1) loose stellate cells with a myxoid background including scattered inflammatory cells (nodular fasciitis-like), (2) spindle cells with a compact fascicular pattern, and (3) sparsely cellular collagenised area, and these may be present within the same case.¹¹

As a result of endoscopic and microscopic features, including size, presence of atypical spindle cells, scattered mitoses and an 'infiltrative' margin, these entities may be mistaken for malignant spindle cell lesions and the differentials considered vary with the site of the lesion.

In the bladder, the main differential diagnoses for IMFT are spindle cell carcinoma, leiomyosarcoma, neurofibroma¹³ and, particularly in adolescents or young children, rhabdomyosarcoma. Although, these tumours are classically said to be distinguishable on morphological grounds (Table 1), the features enabling distinction may be focal and thus not apparent throughout the tumour, or may be partially obscured by a range of inflammatory and reactive infiltrates or by artefacts of processing or fixation.

Immunohistochemistry may be helpful in the differential diagnosis of spindle cell lesions of the bladder, with each entity showing a different immunophenotypic profile (Table 1). However, there is a wide spectrum of possible immunophenotypes for each entity and an individual case may not show the expected 'classical' immunoprofile. For instance, immunocytochemical studies in recent years have shown that IMFT are strongly positive (usually >90% cases) for vimentin and smooth muscle actin (SMA), and variably positive for desmin (0–69%), cytokeratin (20–40%), macrophage marker (KP 1) and CD30, raising the possibility of confusion with spindle cell carcinoma or sarcoma.^{2,10,14,15}

More recently, the presence of anaplastic lymphoma kinase (ALK 1) staining in some cases has been postulated to be of value in the confirmation of IMFT and in its distinction from other entities. A series of studies examining the expression of ALK 1 protein expression by immunocytochemistry or ALK gene rearrangements by fluorescence *in situ* hybridisation (FISH) in IMFT is shown in Table 2.^{5,11,16–19}

The presence of ALK gene translocations involving the 2p23 band, and the subsequent identification of ALK fusion proteins with the protein

Table 1 Spindle cell vesical lesions—morphological features and 'classical' immunoprofile

Entity	Morphological feature	CK	SMA	Des.	Calp	Cald	MyoD1	S100	ALK	
Spindle cell carcinoma	Atypia of surface urothelium, cohesive ‘packets’ of cells, marked pleomorphism, infiltrative margin	+	–/+ (focal, <25% cases)	–/+ (focal, <25% cases)	–	–	–	–	–	
Leiomyo–sarcoma	Parallel bundles of cells, blunt ended nuclei, paranuclear cytoplasmic vacuoles	–/+ (up to 30%)	+	+	+	+	–	–	–	
Neurofibroma	May be polypoid or diffuse (plexiform), wavy nuclei	–	–	–	–	–	–	+	–	
Rhabdomyo-sarcoma	Commonly embryonal type, monomorphous small round blue cells	–/+	–/+	+	–	–	+	–	–/+ (20%)	
IMFT	Mild nuclear pleomorphism, myxoid stroma, inflammatory cells, pushing margin	–/+ (20–40%)	+/– (over 90%)	+/– (0–69%)	+/–	+/–	–	–	+	(33–75%)

CK = cytokeratin, SMA = smooth muscle actin, Des. = desmin, Calpo. = calponin, Cald. = caldesmon.

Table 2 Expression of ALK 1 protein and ALK gene rearrangements in IMFT

Author	Cases	Site	ALK 1 protein expression	ALK gene rearrangement
Cook (2001)	73 IMFT (4 bladder)	Various	60% cases (75% bladder)	—
Chan (2001)	61 IMFT (6 bladder)	Various	8% cases (33% bladder)	—
Coffin (2001)	47 IMFT	Various	36% cases	47% cases
Kutok (2001)	13 IMFT	Spleen, lymph nodes	0% cases	—
Kapusta (2003)	12 IMFT	Kidney	0% cases	—
Hirsch (2003)	23 IMFT	Genitourinary tract	38% cases	0% cases

— = Not studied.

products of the tropomyosin (TPM3, 4) and clathrin heavy chain genes (CLTC) in a proportion of IMFT, is further evidence that a subset of these entities is indeed neoplastic.^{20–22}

The favourable outcome of IMFT in the lung and bladder²³ is well known, however, and even in a wide range of anatomical sites examined, there is a low rate of local recurrence (25%) and no metastases reported (Table 3).^{2,10,15} This indicates that vesical IMFT may be treated with conservative surgical excision compared to that performed with sarcomatous lesions, which may resemble IMFT clinically and radiologically.

We performed a preliminary retrospective immunocytochemical study on nine vesical IMFT and 11 other spindle cell lesions of the bladder, with the aim of assessing ALK1 staining and its value in the distinction of IMFT from other vesical lesions with a similar morphology. Some of the cases were further examined for ALK gene translocations using FISH, and the results were compared with the immunocytochemical expression of the ALK protein.

Materials and methods

Case Selection

Nine cases of vesical IMFT were retrieved from the archives of the histopathology departments involved in the project. A number of other vesical spindle cell lesions, including five spindle cell carcinomas (carcinosarcomas), two leiomyosarcomas, two rhabdomyosarcomas and two neurofibromas were also selected for comparison. The ages and clinical features of the nine vesical IMFT cases are presented in Table 4.

The slides were reviewed by AF and MCP, and one representative block was chosen per case for immunocytochemical examination, including normal urothelium and muscularis propria as internal controls where possible. Serial sections (5 µm) were cut and stained for a pancytokeratin (CAM 5.2 or MNF116), SMA, desmin, ALK 1, calponin and caldesmon and myogenin for the rhabdomyosarcomas, as shown in Table 5.

Immunocytochemical Method

The slides were dewaxed in xylene, rehydrated through graded alcohols and rinsed in water. Antigen retrieval was performed using microwaving or enzyme digestion techniques as shown in Table 4. Endogenous peroxidase activity was blocked for 10 min with DAKO peroxidase block (Catalogue Number S2023). Primary antibodies were then applied for 1 h at room temperature. The stain was amplified using the DAKO ChemMate Peroxidase/DAB kit (Catalogue Number K5001) according to the manufacturer's guidelines. The slides were finally washed in water, taken through graded alcohols and xylene and coverslips applied.

Interpretation of Staining

The staining pattern of the slides was examined using a semiquantitative scoring method by AF and MCP. The slide was scored as 'positive' or 'negative' according to the pattern of staining seen and the extent quantitated as 'focal' or 'diffuse'. The term 'focal' was used to indicate a patchy staining pattern, with <25% of all cells staining with the

Table 3 Studies of outcome in IMFT at various sites, including the bladder

Author	Year	Cases	Site	Mean follow up (months)	Local recurrence (%)	Metastases (%)
Jones	1993	13 IMFT	Bladder	25	0	0
Coffin	1995	84 IMFT	Various	24	25	0
Iczkowski	2001	17 IMFT	Bladder	35	0	0

Table 4 Clinicopathological information for cases of vesical IMFT

Case	Age (Years)	Sex	Size	Treatment	Follow-up
1	50	M	Not known	Cystectomy	—
2	36	F	7.5 cm polyp	Cystectomy	—
3	51	F	Not known	Cystectomy	—
4	13	M	5.3 cm polyp	Partial cystectomy	4 years FOD
5	34	F	4.1 cm polyp	Partial cystectomy	2 years FOD
6	46	M	5.0 cm polyp	Partial cystectomy	2 years FOD
7	33	M	2.0 cm	Partial cystectomy	8 months FOD
8	36	F	4.0 cm	Partial cystectomy	8 months FOD
9	30	M	> 5.0 cm	TUR	5 months FOD

— = follow-up not available, FOD = free of disease, TUR = transurethral resection.

Table 5 Antibodies used in the current study

<i>Antibody</i>	<i>Manufacturer</i>	<i>Antigen retrieval</i>	<i>Antibody dilution</i>	<i>Incubation time (h)</i>
MNF 116	DAKO	10 min CT	1/100	1
CAM 5.2	Becton Dickinson	10 min CT	1/2	1
SMA	DAKO	No treatment	1/150	1
Desmin	DAKO	PH 6.0 MW	1/10	1
ALK 1	DAKO	High pH MW	1/50	1
Calponin	A Menarini	PC	1/3000	1
Caldesmon	A Menarini	PC	1/100	1
Myogenin	DAKO	PC	1/200	1

10 CT = 10 min with 0.1% chymotrypsin (Sigma C4129) at 37°C, pH 7.8; High pH MW = 25 min high power in an 800 W microwave in DAKO target retrieval solution High pH (DAKO S3307), followed by 10 min standing time; pH 6.0 MW = 25 min high power in an 800 W microwave in DAKO target retrieval solution (DAKO S1699), followed by 10 min standing time; and PC = 2 min at full pressure in a 15 lb pressure cooker in 3 l of 0.01 M citrate buffer, pH 6.0.

applied marker, while the term 'diffuse' was used to indicate strong staining in over 25% of cells. The entire slide was examined in an attempt to account for tumour heterogeneity. Positive controls were examined with each batch of stained slides for standardisation of scoring, in addition to the urothelium and muscularis internal tissue controls, and negative controls were performed by omitting the primary antibody.

FISH Protocol

Paraffin-embedded tissue sections were processed using the Vysis Paraffin Pretreatment Kit protocol, substituting xylene in place of the Hemo-De clearing agent. Protease times used were between 30 and 100 min. Slides were denatured in 70% formamide/2 × SSC at 75°C for 6 min followed by dehydration in an ethanol series. FISH was performed with the Vysis LSI ALK probe according to the manufacturer's instructions (Vysis). The probe set contains a 250 bp probe telomeric to the breakpoint region, labelled in Spectrum Orange, and a 300 bp probe centromeric to the breakpoint region, labelled in Spectrum Green. Slides were examined using the BX50 Olympus microscope, equipped with appropriate filters. At least 150 interphases were examined per slide and the percentage of cells showing separation of the probes, reflecting ALK gene translocation, was calculated.

When hybridised with the LSI ALK Dual Color, Break Apart Rearrangement Probe, the 2p23 ALK region in its native state will be seen as two immediately adjacent or fused orange/green (yellow) signals (Figure 2b). However, if a t(2;5) or other chromosome rearrangement at the 2p23 ALK breakpoint region has occurred, one orange and one green signal will be seen, while the native ALK region will remain as an orange/green fusion signal (Figure 2a). The hybridisation result of the LSI ALK Dual Color, Break Apart Rearrangement Probe containing the t(2;5) will be the centromeric green probe remaining at 2p23, while the telomeric orange signal that

covers the region is translocated to 5q35 on the derivative chromosome.

Results

Immunocytochemistry (Table 6, Figure 1)

A positive cytokeratin immunostain was seen in 8/9 (89%) IMFT, all five spindle cell carcinomas (100%) and 1/2 (50%) leiomyosarcomas. SMA was positive in 8/9 (89%) IMFT, 4/5 (80%) spindle cell carcinomas and 2/2 (100%) leiomyosarcomas (Figure 1, Table 1). In contrast, desmin was positive in 7/9 (78%) IMFT, 2/5 (40%) spindle cell carcinomas and 2/2 (100%) rhabdomyosarcomas, but negative in leiomyosarcoma.

Calponin and caldesmon, novel markers for smooth muscle tumours, were positive in 2/2 (100%) leiomyosarcomas, and but also in 8/9 (89%) and 6/9 (67%) IMFT, respectively, indicating their presence in myofibroblasts as well as smooth muscle fibres.

ALK 1 staining revealed a cytoplasmic pattern of staining in 8/9 IMFT (89%), but was not seen in any of the spindle cell carcinomas, leiomyosarcomas or rhabdomyosarcomas examined.

FISH Results

Six IMFT, four sarcomatoid carcinomas and three leiomyosarcomas were examined for ALK gene rearrangements, using the commercial probe kit from Vysis as explained above.

Four of six IMFT (67%) showed ALK gene rearrangements, as characterised by separation of the centromeric and telomeric probes on either side of the common ALK breakpoint region onto different chromosomes, in a range of between 15 and 60% of the tumour cells examined. In contrast, the sarcomatoid carcinomas and leiomyosarcomas examined were completely negative for ALK translocations (Figure 2).

One of the IMFT cases examined revealed an inversion of Chromosome 2 (inv. 2 p23q35) resulting

Table 6 Results of immunocytochemical staining

Type of tumour	Case	CK (MNF116 or CAM)	SMA	Desmin	Calponin, Caldesmon	ALK 1
IMFT	9	8 (5 F, 3D)	8 (5 F, 3D)	7 (all F)	8 (5 F, 3D) 6 (4 F, 2D)	8 (3 F, 4D)
Sarcomatoid carcinoma	5	5 (all F)	4 (2 F, 2D)	2 (1 F, 1D)	—	0
Rhabdomyosarcoma ^a	2	0	0	2	—	0
Leiomyosarcoma	2	1 (1 F)	2 (1 F, 1D)	0	2 (all F) 2 (1 F, 1D)	0
Neurofibroma	2	0	0	—	—	0

F = focal, D = diffuse, — = not done.

^anuclear positivity for myogenin.

Figure 1 An IMFT showing compact fascicles of spindle cells, with an inflammatory component of (a) $\times 200$ magnification (b) and $\times 400$ magnification. (c) Areas of looser spindled cells in a myxoid background are focally seen ($\times 400$ magnification). (d) The ALK 1 immunostain shows diffuse cytoplasmic positivity ($\times 400$ magnification) in the neoplastic cells.

in a variant fusion protein between the ALK gene and ATIC gene. This translocation has previously been reported in anaplastic large cell lymphoma but not, as far as we are aware, in IMFT.

Discussion

IMFT are a group of lesions that arise in a variety of anatomical sites, and are postulated to be aetiologically composed of a variety of entities that may be either neoplastic or inflammatory in nature. The

Figure 2 (a) FISH studies confirm the presence of ALK gene rearrangement in the cells of an IMFT. There is displacement of the green and orange probes against the centromeric and telomeric portion of the common breakpoint region of the ALK gene onto different chromosomes at one allele (white arrow). This shows that part of the ALK gene is translocated from Chromosome 2p onto Chromosome 5. (b) Cells of a leiomyosarcoma show an intact ALK gene at both alleles, with the green and orange probes adjacent to each other (white arrow). This finding confirms that the centromeric and telomeric portion of the ALK gene are on the same chromosome, excluding the presence of a gene translocation at this point.

favourable outcome of most of these lesions, particularly in the lung and bladder is well known, and has implications for initial surgical resection and follow-up. However, the clinical and

radiological similarity of vesical IMFT to sarcomas and spindle cell carcinomas may cause a potential diagnostic problem.

At present, the morphological criteria suggestive of IMFT include a variably cellular spindle cell tumour composed of reactive myofibroblastic cells with elongated nuclei, and the presence of stellate cells, with scattered mitoses but no significant atypia or necrosis. These features are not totally specific to IMFT and may be focally seen in some sarcomas. Electron microscopy is also not definitive, although quantitative differences in cytoskeletal filaments between smooth muscle cells and myofibroblasts may be useful in some cases, and the presence of a fibronexus junction, although rarely visualised by electron microscopy, is also indicative of a myofibroblastic phenotype.^{24,25}

Immunocytochemistry using conventional markers for smooth muscle and epithelial markers has been shown to be positive in a proportion of IMFT, making the evaluation of positive staining for SMA, desmin and cytokeratin unreliable in their distinction from leiomyosarcoma and carcinoma with spindle cell change.

In recent years, ALK 1 has been found to be expressed in the cytoplasm of IMFT in a variable proportion of cases. Studies of ALK 1 protein using immunohistochemical methods have shown positive staining in a range of 0–75% of cases, with high rates of expression in vesical IMFT (33–75%), and complete absence in IMFT of the spleen and lymph nodes.^{5,11,16–18}

The results of our preliminary study using nine vesical IMFT support these findings, with ALK 1 protein immunocytochemically identifiable in eight vesical IMFT (89%), but negative in all 11 sarcomatoid carcinoma, leiomyosarcoma, rhabdomyosarcoma and neurofibromas examined from the bladder. Our results agree with a recent abstract that showed cytoplasmic ALK 1 staining in 12/16 (75%) IMFT, but not in 15 control cases, including leiomyosarcoma, stromal tumours and carcinosarcomas.²⁶

Although a number of cases of rhabdomyosarcoma may show expression of ALK 1, particularly those of alveolar subtype,²⁷ these lesions usually also express desmin and myogenin or myoD1, and show characteristic morphological features that allow identification and distinction from IMFT.

The immunocytochemical ALK 1 protein expression is reflected in the results of the FISH studies. ALK gene translocations were present in a percentage of tumour cells in 4/6 IMFT examined (67%), indicating that a genetic abnormality in the area of Chr. 2p23 often results in overexpression of the ALK 1 protein, and may be an important factor in tumorigenesis of IMFT. In contrast, none of the seven other bladder spindle cell lesions examined showed translocation in the ALK gene, confirming the negative result by immunocytochemistry. The absence of an identifiable ALK translocation in the

remaining two IMFT tested may either reflect the sensitivity of the technique, or be attributed to the fact that the commercial probe used in this experiment only identifies translocations at the most common site of the ALK gene and may not show translocations at other sites. Our finding correlates well with the results of another group, who found 47% ALK gene rearrangement in IMFT,¹⁶ but is in contrast with those of a recent abstract that shows 0% ALK gene rearrangement in 23 genitourinary cases studied.¹⁹ Although the number of cases examined in each category of our study was small, there is no obvious confounding factor in the series of cases examined, and thus no reason why these results may not be extrapolated to a diagnostic setting.

In summary, ALK 1 protein is often upregulated in vesical IMFT by translocation of the ALK gene and is identifiable by immunocytochemistry, making it a valuable marker in cases of IMFT in the bladder. The expression of ALK is not seen in the majority of cases of sarcomatoid carcinomas, leiomyosarcomas or rhabdomyosarcomas of the bladder. Positive ALK 1 immunocytochemical staining, with the conventional morphological and ultrastructural features in current use, may be of value in the distinction of IMFT from other spindle cell lesions of the bladder. The presence of ALK gene translocation may provide further evidence for a neoplastic rather than a reactive or inflammatory nature for the lesion and may be useful in indicating which lesions may show local recurrence potential.

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