

Non-epithelial tumours and non-epithelial tumour-like lesions of the bladder

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Classification (1)

Myofibroblastic proliferations and neoplasms

- Inflammatory myofibroblastic tumour/pseudosarcomatous myofibroblastic proliferation
- Postoperative spindle cell nodule

Benign soft tissue tumours

- Leiomyoma
- Haemangioma
- Neurofibroma
- Schwannoma
- Solitary fibrous tumour
- Paraganglioma
- Granular cell tumour



Classification (2)

Malignant soft tissue tumours

- Leiomyosarcoma
- Rhabdomyosarcoma
- Angiosarcoma
- 'MFH'
- PNET
- MPNST
- Alveolar soft part sarcoma



Classification (3)

Other tumours

- Lymphoma and other haemolymphoid lesions
- Malignant melanoma

Other tumour-like conditions

- Malakoplakia
- Amyloid



Spindle cell lesions of bladder

(Mills *et al.*, 1989)

- "The differential diagnosis of bladder spindle cell lesions is one of the most difficult in surgical pathology and of considerable clinical importance"
- "In view of the diagnostic difficulty it is wise to excise any problematic spindle cell bladder lesion, especially if only limited biopsy material is available"

[although written almost a quarter of a century ago,
remains true today!]



Spindle cell lesions

- Inflammatory myofibroblastic tumour
- [IMT]/pseudosarcomatous myofibroblastic proliferation
- post-operative spindle cell nodule
- Sarcomatoid carcinoma/ carcinosarcoma
- Leiomyosarcoma and other sarcomas
- Other spindle cell lesions e.g. neurofibroma, leiomyoma, solitary fibrous tumour



'Pseudosarcomatous myofibroblastic proliferations' of the urinary tract

– nomenclatures which have been applied to such lesions historically in the literature

- Nodular fasciitis
- Pseudomalignant spindle cell proliferation
- Pseudosarcomatous myofibroblastic tumour
- Pseudosarcomatous fibromyxoid tumor
- 'Inflammatory pseudotumour'



Current nomenclature

- Inflammatory myofibroblastic tumour (IMFT/IMT)
- Pseudosarcomatous myofibroblastic proliferation
- Post-operative spindle cell nodule
- ['Inflammatory pseudotumour' is generally regarded as an umbrella term]



Features of IMT/pseudosarcomatous myofibroblastic proliferation of bladder

- Often sizeable pedunculated mass (except post-operative spindle cell nodule which is typically small)
- Often gelatinous/myxoid
- Frequent involvement of detrusor muscle



Features of IMT/pseudosarcomatous myofibroblastic proliferation of bladder

- 3 histological patterns
 - myxoid vascular
 - compact
 - hypocellular fibrous
- Minimal to absent nuclear pleomorphism, no nuclear hyperchromasia
 - can have scattered 'ganglion-like' cells with prominent nucleoli
 - can have some cells like 'strap cells' (mimic of rhabdomyosarcoma but no cambium layer and myogenin –ve)
- May have mitoses, but no abnormal mitosis
- Small foci necrosis may be seen but no substantial areas of necrosis



Note of caution: similar reaction sometimes seen adjacent to carcinoma (care required in limited biopsies)



Pseudosarcomatous myofibroblastic tumor of the urinary bladder in children

(Hojo *et al.*, 1995)

- Can easily be mistaken for embryonal rhabdomyosarcoma, clinically, radiologically and histologically
- All but 1 [of 11] cases initially diagnosed as sarcoma, usually rhabdomyosarcoma



Inflammatory myofibroblastic tumour/pseudosarcomatous myofibroblastic proliferation of bladder

- 50% cases ALK-1 protein +ve (cytoplasmic)
- ALK-1 translocation demonstrated in about 50% cases (in some series) – gene 2p23 involved
- Alk-1 expression not described in sarcomatoid carcinoma or leiomyosarcoma of bladder but can be seen in rhabdomyosarcoma
- Overlap in cytokeratin expression in all of above lesions but high mol. wt. cytokeratins restricted to sarcomatoid carcinoma



Anaplastic lymphoma kinase 1 (ALK-1)

- Useful in distinction of inflammatory myofibroblastic tumour/pseudosarcomatous myofibroblastic proliferation of bladder (+ve in fewer than 50% of cases) from other spindle cell lesions of bladder
- Cytoplasmic staining
- Expression correlates to some degree with ALK-1 gene rearrangement



Inflammatory myofibroblastic tumors of the urinary tract: a clinicopathologic study of 46 cases, including a malignant example inflammatory fibrosarcoma and a subset associated with high-grade urothelial carcinoma (Montgomery EA et al Am J Surg Pathol 2006;30:1502-12)

- One unique case with features of IMT of bladder with ALK gene rearrangement (but lacking ALK expression by immuno) showed focal overtly sarcomatous areas ('inflammatory fibrosarcoma'). It recurred rapidly and then metastasised causing death.
- No other case described in the bladder has metastasised (these lesions almost always follow a benign course but may recur and may cause obstructive problems if large).



ALK-1 expression in soft tissue lesions:

Expression of Alk1 and p80 in inflammatory myofibroblastic tumor and its mesenchymal mimics Cessna MH et al, 2002

Expression of anaplastic lymphoma kinase in soft tissue tumors: an immunohistochemical and molecular study of 249 cases (Li et al., 2004)

- 14 inflammatory myofibroblastic tumours (IMTs) and 370 other soft tissue tumours studied for Alk-1 expression
- 8/14 soft tissue IMTs +ve
- 10/38 rhabdomyosarcomas +ve
- 35/65 lipogenic tumours +ve
- 6/10 Ewings/PNET +ve
- 4/10 MPNSTs +ve
- 4/28 leiomyosarcomas +ve [1/10 in Cessna paper](but not reported in bladder leiomyosarcoma)
- Leiomyoma 0/10
- 9/48 MFH +ve
- Most tumours other than IMT showed low level expression



Utility of a comprehensive immunohistochemical panel in the differential diagnosis of spindle cell lesions of the urinary bladder Westfall et al. Am J Surg Pathol 2009;33:99-105

- Alk-1 was +ve in 20% of 10 pseudosarcomatous myofibroblastic proliferations and was negative in all (n=22) sarcomatoid carcinoma and smooth muscle neoplasms (n=13)
- CK5/6 and 34BE12 were positive in 27% and 25% sarcomatoid carcinoma but negative in all pseudosarcomatous myofibroblastic proliferations (PMP) and smooth muscle tumours
- p63 was positive in 50% of sarcomatoid carcinoma and focally in 23% smooth muscle tumours but negative in PMPs



Relationship of bladder IMT and IMT of soft tissue?

- Still controversial and not fully resolved
- Bladder lesions more likely to express cytokeratins
- Bladder lesions probably less likely to recur and less likely to metastasise (only 1 reported case), although even in soft tissue cases metastases are rare
- The single case with metastases in the bladder had prior irradiation ?? Could this have been an initiating step in progression to sarcoma



Differential diagnosis of IMT/pseudosarcomatous myofibroblastic proliferation of urinary tract

- Sarcomatoid carcinoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Other mesenchymal tumour e.g. solitary fibrous tumour



Spindle cell lesions of bladder

Good sampling required to look for any areas of carcinoma in situ or conventional invasive carcinoma (features that would support sarcomatoid carcinoma, but may be present only focally)



Myxoid and sclerosing sarcomatoid transitional cell carcinoma: a clinicopathological and immunohistochemical study of 25 cases

(Jones and Young, 1997)



In a child with a myxoid spindle cell lesion in the bladder or urinary tract

- Need high index of suspicion for rhabdomyosarcoma
- Embryonal rhabdomyosarcoma may have areas that are relatively bland cytologically
- Look for cambium layer
- Include myogenin +/- myo D1 in immunohistochemistry panel
- Rhabdomyosarcoma is positive for alpha smooth muscle actin and may be Alk-1 positive
- Heterologous cartilage may occasionally be seen in rhabdomyosarcoma



Leiomyosarcoma of the urinary bladder

(Mills *et al.*, 1989)

- 15 cases – rare tumour but most common bladder sarcoma in adults
- Wide age range
- 8 tumours had 1 or <1 MF/10HPF
- All had infiltrative margins with invasion of detrusor muscle
- 9 had myxoid zones; 6 were mainly or extensively myxoid (haphazard rather than fascicular orientation of fibres when myxoid) – closely resembled IMT, esp. in superficial areas of the tumour
- 3 cases had necrosis
- All alpha-SMA +ve; 8/15 desmin +ve; 12/12 cyokeratin and EMA -ve



Leiomyosarcoma of the urinary bladder

(Mills *et al.*, 1989)

- Mild to moderate nuclear pleomorphism; marked pleomorphism in 4/15 cases
- Myxoid cases had some extravasated erythrocytes + superficial inflammation (appearance v similar or identical focally to IMT); delicate capillary network typically lacking in most leiomyosarcoma (cf. IMFT)
- Preferred to designate lesions when infiltrative (even if <1MF/10HPF) as leiomyosarcoma. Mets rare if <5MF/10HPF)
- Mitotic counts may be underestimated in myxoid areas due to wide cell separation



Leiomyosarcoma of the urinary bladder: a clinicopathological study of 34 cases

Lindberg MR *et al. J Clin Pathol* 2010;63:708-713

“Essentially all urinary bladder leiomyosarcomas are high-grade sarcomas and the diagnosis of a low grade leiomyosarcoma should be made only with trepidation”



Similarities: bladder spindle cell lesions

	Spindle cells	Myxoid	Mitotic figures	Muscularis propria (detrusor) involvement	alpha-SMA	Cytokeratins (broad spectrum e.g. MNF116 or AE1/3 or low molecular weight e.g. CAM 5.2)
IMT	+	+/-	+	+/-	+	+ [50% cases]/-
Sarcoma	+	+/-	+	+/-	+	-/+
Sarcomatoid carcinoma	+	+/-	+	+/-	-/+	+/-



Differences: bladder spindle cell lesions

	Nuclear pleomorphism with hyperchromasia	Abnormal mitotic figure(s)	Large areas of necrosis	Prominent vascular background	In-situ carcinoma +/- obvious epithelial areas	ALK-1 expression	CK5/6	34BE12	p63
IMT	-	-	-	+	-	+/- [<50% cases +ve; some rhabdo +ve]	-	-	-
LMS	+	+/-	+/-	-	-	-	-	-	-/+ [23% focal +ve]
Sarcomatoid carcinoma	+	+/-	+/-	-	+/-	-	-/+ [27% +ve]	-/+ [25% +ve]	+/- [50% +ve]

*Westfall *et al. Am J Surg Pathol* 2009;33:99-105



Use of PAX8 and GATA3 in diagnosing sarcomatoid renal cell carcinoma and sarcomatoid urothelial carcinoma

Chang A. *et al. Hum Pathol* 2013; 44:1563-8.

- For sarcomatoid RCC, PAX8 +ve in 69% (all were GATA3 -ve)
- For sarcomatoid urothelial carcinoma of bladder and upper tract:
 - GATA3 +ve in 31% and 18% respectively;
 - PAX8 +ve in 18% and 4% respectively
- PAX8 was +ve in 1/161 sarcoma cases (Ewings/PNET)
- All 161 sarcomas (various sites) were GATA3 negative
- 1/23 IMTs showed moderate GATA3 +ve (all others and epithelioid AMLs were negative for GATA3 and PAX8)



Neurofibroma of the urinary bladder

Cheng L *et al Cancer* 1999;86:505-13

- 4 cases in Mayo Clinic registry from 1965-1990
- Mean age was 17 (range 7-28)
- All 4 patients had stigmata of neurofibromatosis type 1
- 3 tumours were transmural showing diffuse and plexiform growth
- Bladder atony in 2 patients necessitated cystectomy
- 4th case showed only diffuse mucosal involvement with Meissnerian corpuscle formation
- Mean MiB-1 labelling index was 3.2%
- No malignant transformation with mean follow-up of 9.6 years



Paraganglioma of bladder

- <0.05% of bladder tumours
- Other systemic paraganglioma symptoms in 15% cases
- May have a diffuse growth pattern that can be difficult to recognise as paraganglioma
- Can have a sclerosing pattern that mimics malignancy
- No reliable histological features for predicting malignancy (10% are malignant)



Malakoplakia

McClure J *J Pathol* 1983;140:275-330



Myxoid cystitis with “chordoid” lymphocytes: another mimic of invasive urothelial carcinoma

Hameed O *Am J Surg Pathol* 2010;34:1061-65

- Polyclonal B lymphoid cells with epithelioid morphology arranged in a cohesive cord-like pattern in a myxoid background
- This was initially misinterpreted as recurrent invasive urothelial carcinoma (patient had previous history of invasive high grade urothelial carcinoma)



The nature of atypical multinucleated stromal cells: a study of 37 cases from different sites

(Pitt *et al.*, 1993)

- 10 cases from bladder
- Atypical stromal cells were associated with benign polyps, in peritumoural stroma or following radiotherapy
- No mitoses in any cases
- Mast cells often associated with atypical stromal cells
- Vimentin +ve; desmin +ve only in lower genital tract lesions (not elsewhere)
- Cam 5.2, alpha-SMA, HHF-35, CD68 and S100 –ve
- No myofibroblastic features by EM
- Probably represent a morphological variant of indigenous stromal cells



Detection of residual tumor cells in bladder biopsy specimens: pitfalls in the interpretation of cytokeratin stains

Tamas EF and Epstein JI *Am J Surg Pathol* 2007;31:390-397

- Cytokeratins may be detected in myofibroblastic cells or even smooth muscle cells in the vicinity of a biopsy/TUR site reaction and could be mistaken for residual tumour
- Morphology should be taken into account with concurrent use of alpha-SMA and/or desmin + h-caldesmon in interpretation
- All cases were Alk-1 -ve

