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Intestinal inflammatory myofibroblastic tumour

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Summary

Background. Inflammatory myofibroblastic tumours (IMFTs) are rare tumours characterised by nosologic, histogenetic and aetiopathogenetic controversy and variable clinicopathological features. We report our experience with intestinal-IMFTs (I-IMFTs) that have been reported mainly as single case reports to date.

Methods. Five patients with I-IMFTs, identified between 2005 and 2008, formed the study cohort. The clinicopathological features were obtained from departmental and hospital records.

Results. The median patient age was 13 years. While 4 patients presented with symptoms and signs of intestinal obstruction, one IMFT was an incidental finding at laparotomy for trauma. Three I-IMFTs were located in the small bowel and 2 in the colon. Complete resection with end-to-end anastomoses was performed. The gross morphology included 1 polypoid myxoid tumour that served as a lead point for an intussusception, 3 multinodular whorled masses and 1 firm circumferential, infiltrative tumour.Microscopically, all tumours had typical features of IMFT with variable expression of ALK-1, a low proliferation index and tumour-free resection margins. All patients had an uneventful recovery. One patient was lost to further follow-up. Four patients were well, without local recurrence or metastases at 6 months to 3 years.

Conclusions. Surgery with tumour-free resection margins is the gold standard of care of adult and paediatric I-IMFTs. Heightened recognition of I-IMFT, albeit rare, as a cause of intestinal obstruction, including intussusception, is necessary for preoperative suspicion of I-IMFT.

Since its first description in 1937,[1] the understanding of inflammatory myofibroblastic tumour (IMFT) has evolved from a reactive inflammatory process to a neoplasm of intermediate biological potential.[2-9] Associated with nosologic, histogenetic and aetiopathogenetic controversy, IMFTs occur in all age groups and in diverse body sites, with no definite gender bias.[1,8,10-12] Notwithstanding their existence for more than half a century, gastrointestinal IMFTs are reported rarely. In reporting the clinicopathological features of 5 intestinal IMFTs (I-IMFTs) that were identified in the archives of the University of KwaZulu-Natal teaching hospitals over a 4-year period, we compare and contrast the clinicopathological findings with those recorded globally, and discuss the associated nosologic controversies and aetiopathogenetic advances posed by these heterogeneous spindle cell neoplasms.

Materials

Five patients with I-IMFTs were identified between 2005 and 2008, using the SNOMED word and code search engines. The clinical and gross pathological features were obtained from departmental and hospital records. All resected specimens were fixed in 10% formal saline. Archival haematoxylin and eosin (H & E), immunohistochemical (Table I) and Epstein-Barr virus (EBV) chromogen *in situ* hybridisation (EBER)-stained sections were re-appraised. The retrospective analysis was approved by the institution's bioethics committee.

Results

Clinical features (summarised in Table II)

The age range was 2 - 49 (median 13) years. Clinical intestinal obstruction, suspected in 4 patients, necessitated diagnostic and therapeutic laparotomy, while in patient 5 the I-IMFT was an incidental finding during laparotomy for a traumatic insult. The abdominal X-ray of patients 1, 3 and 4 demonstrated dilated small bowel loops with fluid levels in keeping with intestinal obstruction. The contrast-enhanced abdominal CT scan of patient 1 demonstrated a large homogeneously enhancing left iliac fossa mass that displaced the colon and appeared to encase the sigmoid colon; and that of patient 4 demonstrated a sausage-shaped ileal mass typical of 'ileo-ileal' intussusception (Fig. 1A). While the postoperative course was uneventful for all patients, one patient was lost to further follow-up. The other 4 patients were well, without local recurrence or metastases being recorded in the 6 months to 3 years follow-up period.

Pathological features (summarised in Table II)

Gross pathology: In contrast to the uniform grey-white colour and lack of necrosis in all tumours, there was striking heterogeneity in terms of the architecture and consistency (Table II). The tumours ranged in size from 1.5 to 20 cm in their largest diameters. One tumour (from patient 4) that served as a polypoid lead point of an intussusception had a soft, myxoid consistency with

TABLE I. IMMUNOHISTOCHEMICAL FEATURES OF IMFTS

						Result				
No.	Antibody	Clone	Source	Dilution	Control	P1	P2	P3	P4	P5
1	**MSA**	**HHF35**	**S1**	**1:1000**	**Myometrium**	**1+**	**2+**	**1+**	**3+**	**1+**
2	**SMA**	**1A4**	**S1**	**1:1500**	**Myometrium**	**2+**	**2+**	**2+**	**3+**	**2+**
3	**Calponin**	**CALP**	**S1**	**1:200**	**Myometrium**	**2+**	**2+**	**2+**	**3+**	**2+**
4	**Desmin**	**D33**	**S1**	**1:1000**	**Myometrium**	**1+**	**1+**	**1+**	**3+**	**1+**
5	**Myogenin**	**F5D**	**S1**	**1:100**	**Rhabdomyosarcoma**	-	-	-	-	-
7	**ALK1**	**ALK1**	**S1**	**1:300**	**Anaplastic lymphoma**	**1+**	**1+**	**2+**	**1+**	**1+**
8	**AE1/AE3**	**AE1/AE3**	**S1**	**1:100**	**Skin: epidermis**	**1+**	**1+**	-	**1+**	-
9	**CD34**	**QBEND10**	**S1**	**1:25**	**Skin: Blood vessels**	-	-	-	-	-
10	**S100**	**polyclonal**	**S1**	**1:1000**	**Skin: Nerves**	-	-	-	-	-
11	**CD117**	**C-KIT**	**S1**	**1:500**	**Gastric stromal tumour**	-	-	-	-	-
12	**HHV8**	**13B10**	**S2**	**1:40**	**Kaposi's sarcoma**	-	-	-	-	-
13	**p53**	**DO7**	**S1**	**1:100**	**Nodal lymphocytes**	**1+**	**2+**	**1+**	**1+**	**1+**
14	**Ki67**	**MIB1**	**S1**	**1:40**	**Nodal lymphocytes**	**1+**	**1+**	**1+**	**1+**	**1+**

P = patient; MSA = muscle-specific actin; SMA = anti-smooth muscle actin; S1 = Dakopatts, Carpinteria, Denmark; S2 = Novocastra, Newcastle-upon-Tyne, UK; S3 = Signet Pathology Systems, Inc, Dedham, MA; Immunohistochemical scoring: 1+ = 6 - 25% immunopositivity; 2+ = 26 - 50% immunopositivity; 3+ = 51 - 75% immunopositivity; 4+ = >75% immunopositivity.

TABLE II. SUMMARY OF CLINICOPATHOLOGICAL FINDINGS

	Clinical				Pathological			
P	Age	Gender	Presentation	Outcome	Site	Size (cm)	Appearance	Bowel involvement
1	**13 y**	**Male**	**Fever, LOW, lethargy: 18 m**	**Well: 3 y**	**Jejunum**	**14×9×6**	**Firm multinodular**	**SM, MP, serosa, *mesentery**
2	**2 y**	**Female**	**Constipation:1m; AD: 2 w**	**Well: 1 y**	**Ileum**	**2 cm stricture**	**Ulcero-nodular, firm**	***M, *SM, MP,**
3	**34 y**	**Female**	**Right iliac fossa pain: 1 w**	**LTFU**	**Caecum**	**20×15×18**	**Nodular, soft, myxoid**	***SM, *MP, serosa**
4	**49 y**	**Male**	**Acute abdominal pain, V, D**	**Well: 6 m**	**Ileum**	**3×2, 5×3**	**Polyp, firm, myxoid (f)**	***M, *SM, MP**
5	**3 y**	**Male**	**Laparotomy for trauma**	**Well: 18 m**	**AC**	**1.5×1 × 0.5**	**Polyp, firm, myxoid (f)**	**SM, *MP, *serosa**

P = patient number; M = mucosa; SM = submucosa; MP = muscularis propria; * = dominant tumor site; f = focally; m = month/s; y = year/s; w = week/s; AC = ascending colon; V = vomiting; D = diarrhoea; LOW = loss of weight; AD = abdominal distension; LTFU = lost to follow-up; cm = centimetre /s.

cystic degeneration on cut section (Fig. 1B). Three tumours had a firm, multinodular, whorled appearance on cut section; the largest of these (in patient 3) presented as an ileocaecal mass with dominant mesenteric growth (Fig. 1C). The resection specimen from patient 2 contained a firm, ulcerated, circumferential, transmural infiltrative mass (Fig. 1D).

Microscopic features: All the IMFTs demonstrated a fibromyxoid/vascular pattern characterised by a variable admixture of capillary-calibre blood vessels, inflammatory cells, a plump spindle cell infiltrate and variable fibrosis, myxoid change and oedema (Figs 2 and 3A). The individual spindle cells were randomly disposed or arranged in small aggregates and short fascicles. They contained amphophilic cytoplasm, oval- to spindle-shaped nuclei with vesicular nuclei and variable nucleolar prominence. Stellate and ganglion-like polygonal cells with basophilic cytoplasm were noted focally in all tumours. The inflammatory background comprised lymphocytes, histiocytes, plasma cells and eosinophils and focal lymphoid aggregates in all, and neutrophils in 2 tumours. The mitotic count in all tumours was <3 per 10 high power fields. Hypercellular spindle cell aggregates, atypical mitoses or necrosis were not seen. The spindle cells demonstrated variable immunopositivity with the calponin, anti-smooth muscle actin (Fig. 3B), muscle-specific actin, desmin (Fig. 3C), AE1/AE3, p53, Ki67 and ALK-1 antibodies (Fig. 3D) (Table I). EBER studies were negative in all I-IMFTs.

Discussion

IMFT, a rare neoplasm of intermediate malignant potential that was originally described in the lungs,[2] is typified by a myofibroblastic and mixed inflammatory cell infiltrate.[2,12,13] Disagreement and uncertainty about the histogenesis of IMFTs has resulted in a number of synonyms that include **plasma cell granuloma, plasma cell pseudo-tumour, inflammatory myofibrohistiocytic proliferation, omental-mesenteric myxoid hamartoma** and, most commonly, **inflammatory pseudo-tumour** (IPT).[6,14] While IPT (the original term) encompassed the cellular phenotypic spec-

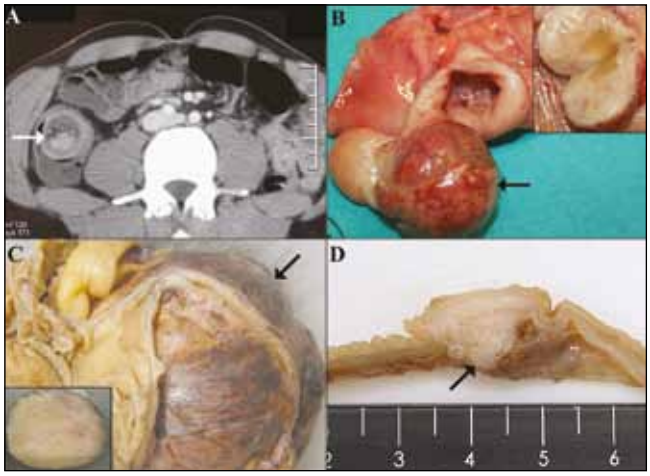

Fig. 1. CT scan demonstrating a sausage-shaped mass (arrow) (A). Polypoid IMFT (arrow) as lead point of intussusception (B) with myxoid degeneration (inset). Ileo-caecal mass (arrow) (C) with a solid, whorled appearance (inset). Firm stricturing mass (arrow) with trans-mural involvement (D).

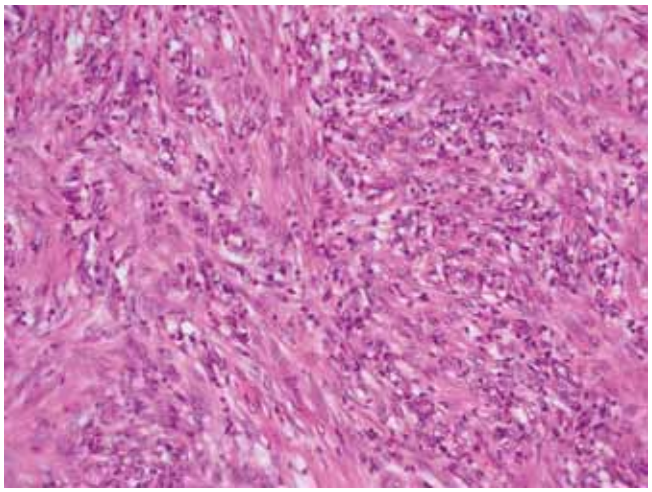

Fig. 2. IMFT displaying a dense, spindle cell myofibroblastic infiltrate with admixed plasma cells, lymphocytes and eosinophils (haematoxylin and eosin (240X)).

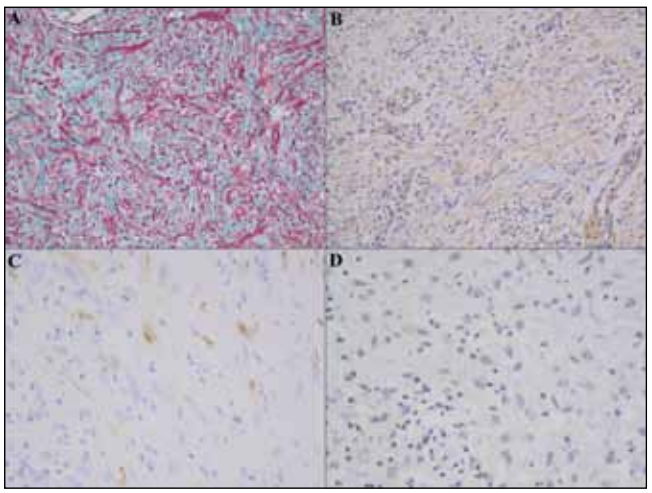

Fig. 3. IMFT demonstrating interstitial fibrosis (A) (Masson trichrome (240X)), anti-smooth muscle antibody (B), desmin (C) and ALK-1 (D) immunopositivity.

trum, including spindle cells, plasma cells, leucocytes and occasional histiocytes, the term 'plasma cell granuloma' was coined to highlight the prominent intratumoral plasmacytic component.[14] The recognition of the myofibroblast as the principal spindle cell type in this tumour resulted in the term 'inflammatory myofibroblastic tumour' being coined in 1990.[15] However, 'inflammatory fibrosarcoma' was proposed in 1991 to describe the presence of cytologically atypical spindle cells and a more aggressive clinical course.[5,16] Despite the controversy over the terminology, definition and criteria used for the diagnosis of IMFT and inflammatory fibrosarcoma,[6,16] there is growing consensus that they are an interrelated myofibroblastic continuum, typified by a spectrum of histomorphological features and potentially aggressive behaviour and shared clinicopathological features.[2,5,12,14,16-20]

The aetiology of I-IMFTs is poorly understood. While some authors propose a neoplastic origin, others believe that it is an immunological response to an infectious[11] or inflammatory process, especially since IMFTs may be seen following abdominal surgery and trauma.[12-14,18,21] While the IMFT in patient 5 was identified at laparotomy for post-traumatic purposes, none of the patients in the present study had a past history of abdominal trauma or surgery. Ancillary histopathological investigations did not demonstrate EBV or human herpes virus 8 staining. Based on the role of oncogenic viruses and cytogenetic abnormalities, including *ALK* gene rearrangements on chromosome 2p23, clonal chromosome abnormalities and DNA aneuploidy,[7] recent literature favours a neoplastic origin for IMFTs.[1,7,17,20,22,23] Over-expression of interleukin-6 and cyclin D1 has also been described.[10,22] While *ALK* gene re-arrangements studies were not undertaken, the present study demonstrated ALK-immunopositivity in all tumours, favouring a neoplastic origin.

While most documented I-IMFTs have been in the small intestine, some have in fact been found on closer examination to be located in the mesentery.[2,11,18,24] Two index I-IMFTs in this small series that demonstrated dominant serosal and mesenteric growth were found to have significant submucosal and muscularis propria bowel wall extension.

The clinical presentation of I-IMFT depends on the region affected.[11,12,18] The onset of the disease may be rapid or insidious.[11] Patients with intra-abdominal tumours may present with an abdominal mass, abdominal pain, vomiting, constipation and bowel obstruction. Children with I-IMFT present with diarrhoea and intestinal obstruction.[11] Systemic features, present in 15 - 30% of symptomatic patients, include fever, weight loss, malaise and night sweats.[22] Four patients in the present study were symptomatic, with abdominal pain and change in bowel habits being the most common presenting symptoms. Although speculative, the lack of symptoms in the fifth patient may be a function of the smaller size and the predominant serosal-based growth. Because I-IMFT was a cause of chronic obstruction in one child and of acute obstruction owing to intussusception in one adult in the present study, these tumours should be considered, albeit rarely, as a cause of intestinal obstruction.

As documented in the literature, there were no specific or characteristic clinical, haematological or biochemical features that could differentiate I-IMFTs from other spindle cell neoplasms.[13,18] Laboratory abnormalities associated with IMFT include hypochromic microcytic anaemia which is usually unresponsive to iron supplementation, thrombocytosis, elevated erythrocyte sedimenta-

tion rate (ESR) and polyclonal hypergammaglobulinaemia, which may resolve after excision of the tumour.[5,12,24] Although not specific to IMFT, these laboratory findings may be used as early indicators of tumour recurrence.[10] While the available radiological investigations confirmed obstructive features and the presence of intra-abdominal mass lesions, neither the origin nor the extent of bowel wall involvement could be confirmed on imaging studies, emphasising the global view that I-IMFTs are not a radiographically distinct entity.[10,18] In contrast, the confirmation of ALK protein or *ALK* gene re-arrangements is useful in distinguishing I-IMFT from other spindle cell neoplastic mimickers that include mainly gastrointestinal stromal tumour (GIST), inflammatory leiomyosarcoma and paediatric congenital/infantile fibrosarcoma. In contrast to IMFTs, GISTs demonstrate CD117 and CD34 immunopositivity.[25] Inflammatory leiomyosarcoma contains fascicles of spindle cells with a dominant smooth muscle immunophenotype whereas the presence of long sweeping fascicles and a 'herringbone' appearance distinguish I-IMFTs from congenital/infantile fibrosarcomas.[26]

While surgery with complete excision is the mainstay of treatment, there are no distinctive clinical, histopathological or molecular markers of recurrence or metastasis.[1,5,8,9,27] Regression following steroid or non-steroidal anti-inflammatory drug use and infliximab has been documented,[19] but the benefit of adjunctive radiotherapy or chemotherapy is unproven.[7,10,11,17,24] Intra-abdominal – specifically intestinal – IMFTs have a propensity for more aggressive clinical behaviour than the extra abdominal lesions.[5] Recurrences appear to be more frequent in extrapulmonary, and especially abdominal, lesions[6,10] that are larger than 8 cm and are locally invasive.[2,12] While most tumours recur within a year of the initial surgery,[18,21] recurrence has been reported 9 years after incomplete resection of the primary tumour.[10] When recurrences occur, complete resection of the recurrences is recommended although spontaneous regression has been reported.[10,12] The occurrence of multiple IMFTs – a rare phenomenon – is purported to be a function of multifocality rather than metastatic spread.[28]

Despite the relatively limited follow-up period of the index patients to date, the lack of recurrences or metastases to date – even of IMFTs with diameters of 14 and 20 cm – strengthens the view that adequate surgical excision is the gold standard in the management of I-IMFTs. The proposed pathological predictors of unfavourable biological behaviour, lacking in the present study, include round cell transformation, a hypercellular proliferative pattern, cellular atypia/nuclear pleomorphism, ganglion-like cell predominance, aneuploidy and p53 over-expression.[12,17,18,21] Furthermore, a low mitotic rate, Ki67 proliferation index and p53 expression were evident in all tumours, congruent with the favourable outcome of the present study. It has been suggested that ALK immunopositivity, noted more frequently in younger patients, may profile tumours with a banal outcome.[7,29] The presence of ALK1 immunopositivity in all I-IMFTs, including those from older patients in the present study, lends credence to this view.

In conclusion: I-IMFT is typified by a spectrum of gross and microscopic features, the key features of which include myofibroblastic proliferation and variable inflammation. Complete surgical excision is the mainstay of treatment. The prognosis is generally good, with only rare reports of malignant transformation, recurrence or distant metastases. Follow-up with long-term clinical and radiological review with serial ESR estimation is advised to ensure early detection of recurrence or metastases.

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