CASE REPORT

Multicentric myofibroblastic sarcoma

Mihir Dilip Wechalekar,¹ Oliver Ayres,² Gelareh Farshid,³ Mark Clayer,⁴ Leslie G Cleland¹

¹Rheumatology Unit, Royal Adelaide Hospital and Flinders University School of Medicine, Adelaide, South Australia, Australia

²Department of Radiology, Flinders Medical Centre, Adelaide, South Australia, Australia

³SA Pathology, and Discipline of Medicine, Adelaide University, Adelaide, South Australia, Australia

⁴Department of Orthopaedics and Trauma, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence to

Dr Mihir Dilip Wechalekar, mihir.w@gmail.com

Accepted 15 October 2014

SUMMARY

We report a case of synchronous, multicentric low-grade myofibroblastic sarcoma presenting in a 62-year-old man. He initially presented with inflammatory symmetric polyarthritis and adhesive capsulitis of his shoulder and hips bilaterally and did not respond to a trial of disease modifying antirheumatic drugs. Over a period of several years he developed progressive restriction of both knees and nodules on his hands, both knees and back. A biopsy of the nodule on his back was inconclusive and subsequent biopsies on his left and then right knee revealed a spindle cell neoplasm with an infiltrative growth pattern, mitotic figures, positive immunostaining for smooth muscle actin and focal myxoid change consistent with myofibroblastic sarcoma. While myofibroblastic sarcoma has been known to metastasise, to our knowledge, a multifocal presentation of this tumour has not been described previously.

BACKGROUND

This is a hitherto unreported presentation of myofibroblastic sarcoma initially presenting with increasing stiffness and mimicking an inflammatory arthritis. This tumour has been known to metastasise but a synchronous multifocal presentation has not been reported.

CASE PRESENTATION

A 62-year-old man, a former clerk, presented to the rheumatology unit in 2006 with several months of symptoms and signs suggestive of inflammatory polyarthritis symmetrically involving the small joints of his hands, left hand extensor tenosynovitis and marked restriction of movements of both hips without significant pain. He had been generally healthy in the past; his family history was negative for neoplasia, inflammatory arthritis or connective tissue disease.

Given his significantly symptomatic symmetric small and large joint arthritis, he was started on triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) for presumed inflammatory seronegative arthritis; this (and a trial of oral prednisolone) was ceased because of lack of benefit.

During 2007–2008 he developed progressive restriction of movement in his knees, further reduction of movement in his hips and restriction of elbow extension bilaterally; generalised joint pain and stiffness continued to be a problem. In early 2010, he synchronously developed firm swellings around the anteromedial aspect of his knees (figure 1) and a firm swelling on his back; he also experienced progressively worsening generalised thickening of both hands (mainly on the palmar

Figure 1 Clinical picture of the swellings on the knee at initial presentation. Note synchronous, symmetric location (arrows).

aspect) associated with non-inflammatory swelling of most of his hand joints with significant functional limitation. The thickening of his palms superficially resembled the thickening seen in Dupuytren's contractures; however, the thickening was more diffuse and contracture was not an obvious feature.

INVESTIGATIONS

Investigations revealed normal blood counts and normal C reactive protein, erythrocyte sedimentation rate and rheumatoid arthritis serology. The patient was found to have IgG κ paraprotein (5 g/L; this has remained stable over the past 2 years). Whole body bone scan revealed moderately increased uptake in the knees, hips, elbows and shoulders. Ultrasonography scan (US) of his hips (when he initially presented) revealed bilateral effusions with communications to periarticular bursae.

US of his knees (performed after he developed synchronous masses around his knees) revealed an unusual picture of fusiform swelling around the semitendinosus and biceps femoris tendons. MRI of his knees (figure 2A, B) was also undertaken and revealed diffuse thickening of multiple fascial structures including the aponeurosis over gastrocnemius, anterior compartment, biceps femoris and pes anserine structures. Positron emission tomography scan (figure 3) revealed patchy ¹⁸F-deoxy-glucose uptake in several areas with putative neoplastic tissue around the knees and pelvis, in addition to shoulders, elbows and hands, involving muscle/musculotendinous structures. MRI of his hands revealed flexor tendinosis, low-grade tenosynovitis

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To cite: Wechalekar MD, Ayres O, Farshid G, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201666

Figure 2 Axial proton density fat-saturated images (initial presentation): right (A) and left (B) knees.

and extensor tendon sheath effusions bilaterally, worse on the right.

Biopsy of his back lesion revealed dense fibrous tissue appearing to entrap fat lobules and despite extensive study and external consultation, no definite conclusion apart from a fibrovascular proliferation of uncertain nature could be reached. A subsequent excision biopsy of abnormal tissue from the anteromedial aspect of his left knee showed a lesion in the same spectrum of a fibroblastic proliferation, with a widely permeative process with abrupt transitions between the paucicellular and more cellular zones (figures 4–7). The latter regions featured mild nuclear atypia and a mitotic rate of up to 7 per 10 high power fields with the tumour cells insinuating between bands of densely hyalinised, sclerotic material. Immunohistochemistry revealed positivity for smooth muscle actin (SMA; Sigma; 1/10 000 dilution; clone 1A4; figure 8), with negative desmin (Novo Castra; dilution 1:200; clone DE-R-11), cytokeratin AE1/3 (Dako; dilution 1:200; clone AE1/AE3), cam 5.2 (Novo Castra; 1:200, clone 5D3), EMA (Dako; 1:200, clone E29) and S-100 (Roche; prediluted; clone 4C4.9) protein expression. β -catenin (Roche, prediluted, clone 14; figure 9) staining was mainly cytoplasmic. CD34

Figure 3 Positron emission tomography (PET) image (coronal).

(Novo Castra; 1:200; clone QBend-10) was only weakly positive. The Mib 1 (Roche; prediluted; clone 30.9; figure 10) index was 10–15%, indicative of a higher proliferative index than expected

Figure 4 Histology of the tumour—low power.

Figure 5 Histology of the tumour—high power.

in the fibromatoses. Fibromatosis was considered as a possibility but the morphology and the multifocality of disease distribution did not support this diagnosis.

DIFFERENTIAL DIAGNOSIS

A range of differential diagnoses were considered, including fibromatosis and other sarcoma subtypes. Notwithstanding the unusual presentation and the apparent multiplicity of lesions, the morphology and immunoprofile were regarded as showing features of a sarcoma with fibroblastic and myofibroblastic differentiation. Further consultation supported the diagnosis of a low-grade myofibroblastic sarcoma. Subsequently, an excision biopsy of tissue from the anteromedial aspect of his right knee was performed. This revealed similar findings to the contralateral side. The palmar thickening was difficult to explain on the basis of the available biopsy reports, but was thought to be aetiologically similar.

TREATMENT, OUTCOME AND FOLLOW-UP

In addition to the aforementioned synchronous masses over the anteromedial aspects of the patient's knees, during the next several months he synchronously developed similar masses in relation to the posterolateral aspect of both knees; these were excised as well and revealed findings similar to the anteromedial tumours. Additional staining for specific mutations including ALK, c-kit and CD45 was negative. He is currently being

Figure 7 Whorls and fascicles of tumour cells and gaping vessels.

followed up clinically, and while there have been no recurrences in the areas operated on previously, he has had a new primary lesion (confirmed as similar to previous lesions on excision biopsy) in his right sartorius muscle.

DISCUSSION

Myofibroblasts, which are modified fibroblasts, are found in the stroma of some normal tissues and are the principal cell type in some reactive and neoplastic soft tissue lesions.¹ Myofibroblasts are spindled, spindle-shaped or stellate cells with sparse to moderate cytoplasm and an indistinct border.¹ They have similar synthetic machinery as fibroblasts, but also possess myofilaments as seen in smooth muscle cells. The myofilaments in myofibroblasts are peripheral and reduced in numbers as compared to those in smooth muscle cells.² Myofibroblasts have a fibronexus: a cell-stromal attachment that, while distinctive, is not unique to myofibroblasts.^{1 2} Myofibroblasts are components of reactive processes such as nodular fasciitis and granulation tissue; they are also found in non-metastasising neoplasms such as fibromatoses and myofibroblastomas.² In part a reflection of controversies pertaining to myofibroblast identification and neoplastic transformation of myofibroblasts, myofibroblastic sarcomas were first described relatively recently by Mentzel *et al*,³ who first reported 18 cases with distinctive morphological and immunohistochemical characteristics, and established diagnostic criteria. Of these, eight myofibroblastic sarcomas were intramuscular or extended into skeletal muscle and three were located in

Figure 6 Low power view of the interface between dense collagenous areas and cellular zones of the tumour.

Figure 8 Smooth muscle actin positivity.

Figure 9 Staining with β -catenin.

Figure 10 Staining with Mib-1 antibody.

perifascial tissues. Tumour cells were spindle shaped, diffusely infiltrative, had fusiform nuclei and poorly defined cytoplasm and were set in a collagenous matrix; they stained positive for at least one myofibroblastic marker on immunohistochemistry.³ Follow-up of 11 of the patients in this case series found metastases (distant soft-tissue, intraosseous and pulmonary) in one patient and local recurrence in two patients. Reactivity with β -catenin is usually observed in fibromatoses and also in a proportion of myofibroblastic sarcomas.⁴ The same immunohistochemical markers can be positive in benign and malignant myofibroblastic lesions, and only subtle differences in cellularity, histology and nuclear morphology may distinguish benign and malignant lesions.⁵ Until recently, the concept of a sarcoma composed predominantly or exclusively of myofibroblasts was thus questioned.⁵

Low-grade myofibrosarcomas (LGM) are spindle cell neoplasms. Their usual site of occurrence is deep soft tissue, but some occur in the subcutis or submucosa. Their growth pattern is that of unencapsulated tumours, which often infiltrate adjacent fibrous tissue, fat or skeletal muscle.¹ As described above, LGMs invade locally and are known to metastasise or progress to high-grade sarcoma,² but to our knowledge, multifocal presentation has not been described.

The unusual clinical presentation of this patient raised several other diagnostic possibilities including fibromatoses/myofibromatoses (though these may be superficial or deep, they are usually localised and not multifocal).² Nodular fasciitis and proliferative fasciitis were further differential diagnoses (though these are usually solitary rather than multifocal), as was a paraneoplastic phenomenon secondary to a circulating stimulus. Lastly the multifocal nature raised the possibility of an underlying predisposing genetic mutation; or metastatic carcinoma (although the symmetric nature is against the latter). The usual treatment of choice for myofibrosarcomas is local excision; about a third recur locally.¹

In conclusion, we report a myofibroblastic sarcoma that presented with synchronous multifocal involvement, which to our knowledge has not been previously reported. The rarity of the condition, its insidious onset and multifocal nature with only subtle differences in pathology to guide benign from malignant, as well as lack of definitive treatment when multifocal, make this a challenging condition to diagnose and treat. Our case demonstrates that surgical treatment of marginal excision with preservation of function can provide long-term survival with preserved function, and should provide an indication of how to treat this rare condition.

Learning points

- ▶ Low-grade myofibroblastic sarcoma can present synchronously.
- ▶ Diagnosis of these conditions can be challenging because of their diverse presentation, slow growing nature and inherent difficulties in histological diagnosis.
- ▶ Importantly, surgical treatment of marginal excision with preservation of function can provide long-term survival and function. It is notable that our patient remains relatively well and ambulant in spite of multifocal disease with postural changes and moderate disability.

Acknowledgements The authors gratefully acknowledge the contribution of Professor Christopher Fletcher, Harvard Medical School to interpretation of the histology.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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