Recurring digital fibroma

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SUMMARY Seven cases of recurring digital fibroma were seen over a 35-year period. All demonstrated the classical clinical, macroscopic, and microscopic features of this distinct tumour, including the pathognomonic round, eosinophilic cytoplasmic inclusion bodies. Ultrastructurally, all seven cases were confirmed to be myofibroblastic in nature, and the morphology and intracellular topography of the inclusion bodies suggested their derivation from contractile protein. These findings establish recurring digital fibroma as a neoplastic lesion of the myofibroblast.

Recurring digital fibroma (RDF) was first described and characterised by Reye. The prevalence of the tumour is difficult to assess, but it is probably quite rare. We reviewed the pathology files of the Children’s hospital at Yorkhill and uncovered six cases of RDF. A seventh case was added to the series from the pathology files of the Mater Misericordiae Hospital, Dublin. Reye was first to identify the pathognomonic feature of this tumour by light microscopy. This is the presence of rounded eosinophilic cytoplasmic inclusions within the tumour cells. The latter are plump spindle cells arranged in bundles of interlacing fascicles in a collagenous background. The nature of the cytoplasmic inclusions has been the subject of considerable research. Their appearance in haematoxylin and eosin-stained sections is suggestive of viral-type inclusions, and ultrastructural and virological investigations have been directed towards identification of a virus in these lesions. All of these investigations have been uniformly negative in this regard. It was not until 1979 that attention was specifically directed to the ultrastructural features of the constituent cells of this tumour in addition to the features of the inclusions. This report was followed in 1980 by a similar ultrastructural analysis of three further cases.

We now report the microscopic and ultrastructural findings in seven further cases of RDF. From our ultrastructural findings, it is apparent that the component cells of this tumour are myofibroblasts, as previously suggested. This brings the total number of such documented cases to date to eleven.

No evidence of viral structures was found in any of the cases in this series, and this observation conflicts with previous reports. However, the morphology and intracellular relationships of the intracytoplasmic inclusions is suggestive of their derivation from contractile protein.

Material and methods

CASES

Examination of the laboratory records of the Royal Hospital for Sick Children, Glasgow between 1947 and 1981 revealed a total of six cases of RDF. A seventh case was retrieved from the files of the Mater Misericordiae Hospital Dublin, and is incorporated in this project by kind permission of Drs P Dervan and S O’Loughlin. These cases are numbered in the Table. Cases 1–5 occurred between 1947 and 1953, and all had been fixed in mercuric fixatives and embedded in paraffin blocks. Case 6 was fixed in buffered 10% formalin and case 7 was fixed in unbuffered 10% formalin. The blocks of all cases were retrieved, recut and restained.

ELECTRON MICROSCOPY

Tissue for electron microscopy was obtained from cases 1–5 from the paraffin blocks. Unprocessed tissue from cases 6 and 7 (formalin-fixed) was available for electron microscopy. All tissues (including those retrieved from paraffin blocks) were post-fixed in osmium tetroxide prior to staining with uranyl acetate and lead citrate for electron microscopy.

Results

CASES

Details of the seven cases in this series are presented in the Table. Despite the title of this tumour,
Clinical data of seven cases of RDF

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Duration of tumour</th>
<th>Location</th>
<th>Treatment</th>
<th>Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 yr</td>
<td>M</td>
<td>Present since birth</td>
<td>4th left finger</td>
<td>Local</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>9 yr</td>
<td>F</td>
<td>Present for 6 months</td>
<td>4th left toe</td>
<td>excision</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>1 yr 7 months</td>
<td>F</td>
<td>Present for 1 month</td>
<td>2nd and 3rd right toes</td>
<td>in</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>1 yr 2 months</td>
<td>M</td>
<td>No details</td>
<td>3rd left toe</td>
<td>all</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>9 months</td>
<td>M</td>
<td>No details</td>
<td>Toe</td>
<td>seven</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>5 months</td>
<td>M</td>
<td>Present for 3 months</td>
<td>5th right toe</td>
<td>cases</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>7 months</td>
<td>M</td>
<td>No details</td>
<td>2nd left toe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Troublesome recurrences occurred in only one case (case 1). The ages of the patients ranged from 5 months to 9 yr, with a mean age at presentation of 3 yr 5 months. The male:female ratio in this series is 5:2. Six cases involved toes other than the first which was not involved; one (case 1) involved the fourth left finger. This age and topographic distribution, which excludes the thumb and big toe, is characteristic of RDF.

Macroscopic examination
Grossly, all lesions measured less than 1.5 cm in diameter. The appearance of the tumour in case 6 is shown in Fig. 1.

Light microscopy
All lesions were cellular and composed of bundles of plump spindle cells arranged in whorling interlacing fascicles. The tumours extended from below the basal layer of the epidermis, which showed loss of rete ridges, to the deep level of excision (fascia or periosteum, Fig. 2). High power analysis (Fig. 3) revealed the characteristic, eosinophilic round cytoplasmic inclusion bodies (one indicated by arrow). Haematoxylin and eosin ×560

Fig. 1 Gross appearance of the tumour on the anterior and medial aspects of the left fifth toe in case 6. This tumour measured 1.5 cm (max diam)

Fig. 2 Low-power micrograph of case 5 showing a spindle cell tumour occupying the dermis. Note the loss of rete ridges in the overlying epidermis and the typical pattern of interlacing fascicles of tumour cells. Haematoxylin and eosin ×90

Fig. 3 High-power photomicrograph of case 5 showing bundles of plump spindle cells, many bearing round cytoplasmic inclusion bodies (one indicated by arrow). Haematoxylin and eosin ×560
plasmic inclusion bodies, which were readily seen in all cases with routine haematoxylin and eosin staining. There was no evidence of malignancy in any of the tumours in this series.

Connective tissue stains showed that the tumour background was collagenous. The cytoplasmic inclusions stained intensely purple with PTAH, yellow with MSB, and red with Masson's trichrome. The cytoplasmic inclusions are orthochromatic with toluidine blue and negative with periodic acid-Schiff (PAS). Viral stains (phloxine tartrazine, feulgen, and methyl green pyronine) failed to stain the cytoplasmic inclusions.

**Electron microscopy**

Ultrastructural analysis of all cases yielded similar results (Figs. 4–6). The cells were seen to be elongated, with nuclei which were frequently irregular in outline. The cytoplasm showed abundant rough endoplasmic reticulum, occasionally with foci of intracellular collagen synthesis within endoplasmic reticulum. In addition, there were bundles of microfibrils with interspersed dense bodies running in the long axis of the tumour cells. Frequently, beneath the cell membrane, collections of micropinocytotic vesicles were noted. The external environment was intensely collagenous. These features identify the cells of the tumours as myofibroblasts, although basement membrane material was not identified in any of the cases. This feature is probably explained by suboptimal fixation.

The cytoplasmic inclusions were rounded, non-membrane bound, electron-dense bodies with a distinctly fibrillar structure. This latter feature was most evident at the edges of the inclusions. Occasional membrane-bound vacuoles were noted within some of the inclusions. A striking feature in many cells was the intimate relationship of bundles of microfibrils, with their attendant dense bodies, to the cytoplasmic inclusions. In some instances, this feature was so striking as to impart a cartwheel appearance with the inclusion centrally placed and the microfibrils appearing to radiate from the inclusions in a radial or spoke-like manner (Fig. 6). This
Fig. 5  Case 7: this electron micrograph shows another inclusion-bearing tumour cell with two parallel bundles of microfibrils (F) with dense bodies (D) almost surrounding the nucleus (N). As in Fig. 4 these microfibrils merge with the electron-dense inclusion (I), which also shows a fibrillar structure and contains a number of vacuoles. Endoplasmic reticulum (ER) is present between the nucleus and the cytoplasmic inclusion, and extracellular collagen (C) is also present. Uranyl acetate and lead citrate ×12 144

Fig. 6  Case 7: this electron micrograph emphasises the continuity between the cytoplasmic inclusion (I) of a tumour cell and the cytoplasmic microfibrils (F). Cigar-shaped dense bodies (D) and extracellular collagen (C) are again obvious. Multiple vacuoles are apparent within the inclusion. Micropinocytotic vesicles are present at lower right (P). Uranyl acetate and lead citrate ×16 380
Recurring digital fibroma

Discussion

Seven cases of RDF are presented in which the clinical and light microscopic features concur with previous descriptions. The ultrastructural features of the tumour cells lead to the conclusion that these tumours are derived from myofibroblasts. Although the ultrastructural features of the inclusions are well known, this latter suggestion has previously been made in only two papers citing only four cases. Our series brings the total number of documented cases of myofibroblastic histogenesis to 11. In addition, the general morphology and intimate spatial relationship between the inclusions in the cytoplasm of the cells and their microfibrils is such as to suggest that the inclusions may be derived from contractile protein, possibly of Z line origin. A possible mechanism for this derivation could be an enzymatic abnormality accompanying neoplastic transformation of myofibroblasts, as has been suggested, and this proposition is further supported by the recent demonstration of the proteinaceous nature of the inclusions. This requires further investigation and the recent excellent tissue culture work of Miyazono will undoubtedly help bring this line of research to fruition. As in earlier studies, no evidence of a viral aetiology was noted.

The history of the myofibroblast is very recent, and has been reviewed by Majno and more recently comprehensively summarised by Lipper et al. and Seemayer et al. These latter papers summarise the possible role of myofibroblasts in various physiological and pathological situations. To date, no convincing evidence has been put forward to suggest that there is a primarily neoplastic abnormality of myofibroblasts, although these cells have been noted in the desmoplastic reactions within and around many carcinomas and sarcomas. This impression has recently been reaffirmed by Seemayer et al., although they acknowledge the dubious claims of others to the contrary. Thus, the so-called RDF is the first genuine neoplastic transformation of the myofibroblast.

It is opportune to cite a recent case report of a tumour identical by light and electron microscopic criteria occurring in a 44-year-old man on the upper arm. This is the first such report and casts some doubt on the age and topographic distribution of RDF. Thus, it is inappropriate to continue to apply adjectives such as infantile, digital, or recurrent to this tumour. A strictly descriptive term should be considered which would be specific enough to represent this entity without attempting to limit the tumour to a particular age group or topographic distribution. We suggest "Inclusion body myofibroblastoma" is a suitable title.

Having established the myofibroblast as the cell of origin of this tumour, it is hoped that study of further cases may lead to improved understanding of the myofibroblast, as it can now be investigated from the angle of neoplasia, as well as in relation to reactive pathological and physiological functions. Consideration and expansion of concepts surrounding myofibroblasts will be rewarded by greater understanding of wound healing and host responses to neoplasia.

We wish to thank the technical staffs of our laboratories for assistance with light and electron microscopy, Mr T Parker and Mr F Coleman for most of the photographs and Dr P Dervan and Dr S O'Laughlin for permission to use case 7 in this study. We also thank Dr AK Watters for assistance with interpretation of the electron micrographs and Mrs M Thomson for typing the manuscript. Dr BF Boyce provided much useful criticism of the paper.

References


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