New look at mesoblastic nephroma

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SUMMARY Thirty eight mesoblastic nephromas were studied. The age range of the patients was between the neonatal period and 18 months. The presence of cartilage is consistent with a mesoblastic origin, but squamous epithelium was a feature in three tumours.

Particular attention was given to the adjacent renal tissue in which various histological features were noted: vacuolated and dysplastic tubules; cysts; and subcapsular epithelial tumourlets. The findings had aspects in common with both dysplastic kidneys and nephroblastoma. Classification of the tumours as normocellular and hypercellular was attempted, but there was considerable overlap.

The behaviour of the tumour was good in all cases, although follow up was relatively short on some patients, and deaths from non-neoplastic causes occurred.

The term mesoblastic nephroma was introduced¹ to imply a relatively differentiated neoplasm predominantly composed of spindle shaped mesenchymal cells, the presence of cartilage being noted in some cases. Inflammatory response to the tumour has not been regarded as a feature, although haemopoiesis may be present. The histological appearances have been described as fibroblastic or leiomyomatous, or both.² The cells at ultrastructural level are consistent with fibroblasts, although the microfibrillary structure may suggest a smooth muscle or myofibroblastic origin.³ It has been suggested⁴ that the tumour arises from secondary rather than primary mesenchyme—namely, from tissue that is no longer capable of producing tubular epithelial cells. The young age at presentation of the neoplasm, together with immune

studies using fibronectin and laminin⁵ do not lend support to this hypothesis.

Material and methods

Tissue or paraffin sections from the 38 tumours were obtained as follows: Manchester Childrens' Tumour Registry, group A (5); United Kingdom Childrens' Cancer Study Group, group B (14); Children's Hospital, Columbus, Ohio, group C (9); and HB Marsden, group D (10). A variable number of slides were available from each case, haematoxylin and eosin preparations being made on all tumours; trichrome and reticulin stains when unstained sections or tissue were received.

The Table shows the ages of the patients in the Manchester Children's Tumour Registry together with the figures for the other types of primary renal neoplasm included in the registry. The overall age in this series ranged from the neonatal period to 18

Accepted for publication 23 December 1985

Renal tumours obtained from Manchester Children's Tumour Registry 1954-1983

Age at presentation (months)	Mesoblastic nephroma	Wilms' tumour	BMRTC*	Rhabdoid renal tumour	Renal carcinoma	Unbiopsied renal tumours	Total
1-2	4	1					5
3-5	1	3		1			5
6-11		19	1				20
12-23		30	3	1			35
24-59		72	1		1	4	78
60+		26	1		4		31
Total	5	151	6	2	5	5	174
(%) all renal tumours (with known histology)	3.0	89.3	3.5	1.2	3.0		

*Bone metastasising renal tumour of childhood.

Fig. 1 Mesoblastic nephroma with short spindle cells showing haphazard arrangement. (Haematoxylin and eosin) $\times 250$.

months. The patients from groups C and D tended to be younger than those in groups A and B, 16 of the 19 tumours coming from neonates.

Two of the neoplasms were diagnosed at necropsy, one in an infant with hyaline membrane disease. The other was a premature neonatal death. There had been polyhydramnios in the pregnancy. The association between polyhydramnios and mesoblastic neph-

Fig. 3 Subcapsular band of normocellular mesoblastic nephroma. (Haematoxylin and eosin) $\times 100$.

roma has been recorded on more than one occasion.^{6,7} Two other children died, one with septicaemia in the first year of life and the other with microcephaly and hemihypertrophy (referred by Anne O'Meara, Dublin). There was no evidence of aniridia in the second case. Recurrence of tumour, or metastasis, were not recorded in any of the patients, although follow up was relatively short for some of them.

Fig. 2 Normocellular mesoblastic nephroma with densely cellular area. (Haematoxylin and eosin) $\times 100$.

Fig. 4 Bands of normocellular mesoblastic nephroma and large vascular channels in perirenal fat. (Haematoxylin and eosin) $\times 100$.

Fig. 5 *Mesoblastic nephroma with islands of pre-cartilage. (Haematoxylin and eosin) $\times 250$.*

Results

The tumours showed variable features: long spindle cells, sometimes arranged in fascicles and resembling leiomyoma; shorter spindle cells with a more haphazard arrangement (Fig. 1); and also looser areas with polygonal and stellate cells. In one neoplasm a typical storiform arrangement suggested histiocytic features. The degree of cellularity was variable and we

Fig. 6 *Mesoblastic nephroma with differentiated squamous epithelium. (Haematoxylin and eosin) $\times 250$.*

Fig. 7 *Normocellular mesoblastic nephroma with dysplastic tubules. (Haematoxylin and eosin) $\times 100$.*

attempted to classify the tumours as either normocellular (10) or hypercellular (21). Some overlap occurred, however, and the remaining seven neoplasms showed a mixed degree of cellularity.

Most of the normocellular tumours occurred in younger children (seven of 10 neonatal), but the three others occurred in patients of 2 months, 10 months, and 1 year of age, respectively. The children with hypercellular mesoblastic nephroma were, on the whole, older, and the four over 1 year of age were placed in this group. There were, however, seven infants in the neonatal period who had hypercellular neoplasms. The mixed tumours were virtually confined to the neonatal period with only one older infant of 5 months.

The degree of cellularity seen in the hypercellular tumours was variable, sometimes very dense and virtually indistinguishable from blastema as shown in a neonatal case (Fig. 2). Mitotic figures up to 4/high power field were noted in both hypercellular and normocellular areas. Cellular reaction, predominantly lymphoid but with other cell types including eosinophils, was noted in some neoplasms as were foci of haematopoiesis.

SUBCAPSULAR AND PERIRENAL EXTENSION

A feature of two of the mesoblastic nephromas was the presence of extensive subcapsular bands of tumour (Fig. 3). These seemed to be connected to the main mass. More commonly, bands projected into the perirenal fat (Fig. 4). These extensions were always normocellular and were associated with large thin

Fig. 8 Subcapsular epithelial tumourlet from a case of mesoblastic nephroma. (Haematoxylin and eosin) $\times 100$.

walled vascular channels. Such spaces were noted in the more central portions of several neoplasms but were more prominent at the periphery and were sometimes present outside the tumour without extrarenal extension of the tumour.

CARTILAGE

Cartilage or pre-cartilage was noted in six of the mesoblastic nephromas (Fig. 5). Five of these were

Fig. 9 Glomerular cysts and dysplastic tubules from a case of mesoblastic nephroma. (Haematoxylin and eosin) $\times 100$.

Fig. 10 Vacuolated cortical tubules with basal nuclei from a case of mesoblastic nephroma. (Haematoxylin and eosin) $\times 400$.

from neonates, one being a 7 month premature neonatal death and another a five month infant.

SQUAMOUS EPITHELIUM

Squamous epithelial islands were present in three neoplasms, although always as a minor feature, and only one focus was found in any particular tumour (Fig. 6). The epithelial tissue was highly differentiated, showing cornification, and was only present in association with cartilage. We are aware, however, of an additional mesoblastic nephroma containing squamous epithelium without the presence of cartilage. (AJM Van Unnik, personal communication). Two of the infants whose tumours contained squamous epithelium were neonates and the third was the 5 month old infant (preceding paragraph).

DYSPLASTIC TUBULES

Irregular tubules with tall hyperchromatic epithelial linings were recorded in nine neoplasms (Fig. 7). They were sometimes large and dilated, being present in the substance of the tumour but also in the associated renal parenchyma. All 10 patients whose tumours showed this feature were in the neonatal period, with the exception of the 5 month old infant whose mesoblastic nephroma contained cartilage and squamous epithelium.

EPITHELIAL TUMOURLETS

In two of the patients, both in the neonatal period, epithelial tumourlets were found in the subcapsular region. In both of these tumours dysplastic tubules

Fig. 11 *Multinucleated cells with abundant cytoplasm, possibly of myoblastic origin in mesoblastic nephroma. (Masson's trichrome.) × 400.*

were recorded. The nodules produced a bulge in the capsule and comprised two to seven tubules of varying size, possessing tall hyperchromatic columnar epithelium (Fig. 8).

CYSTS

Cysts were found in nine of the tumours and were both tubular and glomerular. The tubular cysts had cuboidal or flattened lining cells and were seen in both tumour and renal parenchyma, whereas the glomerular cysts were confined to the renal parenchyma alone (Fig. 9).

VACUOLATED TUBULES

In seven cases the renal parenchyma showed the presence of vacuolated cortical tubules. The cells were swollen with wisps of eosinophilic material and basally situated nuclei (Figs. 3, 9, and 10). The appearances were consistent with a degenerative change, and in some places enlarged distorted cells were barely recognisable as being of tubular origin. Vacuolated tubules were not seen in the substance of the tumour.

UNCLASSIFIED CELLS

Large eosinophilic multinucleated cells were recorded in one tumour (Fig. 11). These were considered to be rhabdomyoblastic in origin, and the slide was decolourised and then stained for myoglobin using the immunoperoxidase method. Results were negative, although myoglobin is one of the less commonly positive markers for muscle in tumours, and the material had received less than ideal treatment.

ADRENAL CYTOMEGALY

In one case cytomegaly of the fetal adrenal cortex was found (referred by Janice R Anderson, Cambridge).

Discussion

The variation in histological features seen in this series raises the question as to whether all 38 tumours should be placed in the same group. The variation between normocellular and hypercellular tumours does not present a problem, as there was considerable overlap between the two types. The different cell types seen in some neoplasms also supports the suggestion that they belong to one group, although some difficulty might be experienced with the neoplasms that may have some histiocytic features, particularly storiform arrangement.

The overall incidence of 3% of childhood renal tumours for mesoblastic nephroma as shown in group A is similar to that of 2.7% taken from a study of 250 childhood renal neoplasms.³ In that series the figure of 13% of renal tumours in the first year of life corresponds to that of 17% in group A. The youngest patient with a Wilms' tumour in group A was 2 months old, whereas four of the five mesoblastic nephromas came from younger children.

There was some correlation between cellularity of the mesoblastic nephroma and age of the patient. All the patients over 1 year old had hypercellular tumours, although four such neoplasms were seen in neonates, and the mixed degree of cellularity tumours was almost exclusively found in young infants.

The presence of cartilage and also osteoid has been recognised in mesoblastic nephroma.³ Cartilage was noted in nearly 16% of the tumours in the present series and is consistent with a mesoblastic origin for the neoplasm. The finding of squamous epithelium in three cases with knowledge of a fourth militates, however, against a purely mesoblastic nature. The presence of mature myocytes in mesoblastic nephroma has been considered,⁸ and the rarity of cells possibly conforming to this type, together with the isolated examples of squamous differentiation in the present series, indicate that such differentiating features may not be apparent without detailed and careful examination of the material.

Bizarre and dysplastic tubules differing from entrapped normal nephron units at the periphery have been described in mesoblastic nephroma.⁹ Such tubules were not confined to the tumour itself in the present series and were also noted in the adjacent renal parenchyma. A more striking feature was the presence of subcapsular epithelial tumourlets that may represent a neoplastic potential, not only as regards mesodermal, but also as metanephric elements in mesoblastic nephroma.

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The vacuolated tubules in the renal parenchyma may have similar implications to the dysplastic changes. The presence of non-specific "foam-cell" changes in tubular cells in the Drash syndrome⁹ may be a basic embryogenic abnormality with impaired cellular organisation at a critical developmental stage.

Cysts, both glomerular and tubular, were noted in nearly one third of tumours in the present series, and cysts, dysplastic tubules, and cartilage are prominent features of multicystic dysplastic kidneys.

It has been suggested that the dysplasia in mesoblastic nephroma is the result of mechanical disturbance in the growth and development of the nephrons. Similarly, tubular and glomerular dysplasia have been regarded as the effects of obstruction and not as signs of neoplasia.⁷ This interpretation of the findings may not be correct. The dysplastic tubules in multicystic kidneys may not be due to obstruction, and the epithelial tumourlets associated with mesoblastic nephroma are unlikely to have such a method of production. It is equally possible that the tumour provides a link between dysplasia and higher degrees of renal neoplasia.

The presence of blastemal areas, epithelial tumourlets, squamous epithelium, and possibly striated muscle indicates that Wilms' tumour is the malignant counterpart of the mesoblastic nephroma. The association with hemihypertrophy, microcephaly, and adrenal cytomegaly in this series may also lend some support to such a suggestion. In addition, umbilical hernia was recorded in one of the cases. The age incidence of the two neoplasms has a striking correlation. No child with nephroblastoma in group A was under 2 months of age, the peak incidence of mesoblastic nephroma occurring in younger infants and tailing off as that of the Wilms' tumour increased.

The suggestion that the bone metastasising renal tumour may be the malignant counterpart of the mesoblastic nephroma¹⁰ seems less likely. Only two of 60 studied cases of bone metastasising renal tumour were from children under 1 year old who presented towards the end of that period, and the same overlap of incidence with mesoblastic nephroma, as was the case with Wilms' tumour did not occur. Furthermore, histological similarities between the two tumours were not found in the present series.

None of the cases in this study showed evidence of nephroblastomatosis, and from an examination of so many cases this would tend to exclude such an association.

There was little evidence of continuing nephropathy in any of the patients, although hypertension

was recorded as a feature in one case. There was no residual tumour to suggest increased renin production as a possible cause.¹¹

The nature of the mesoblastic nephroma, together with its possible association with dysplasia and nephroblastoma provide important fields for future study. From an assessment of the cases in this review it would seem advisable to make a detailed histological examination of such neoplasms and to pay particular attention to changes in the associated renal parenchyma. We also suggest that the term mesoblastic may not be entirely appropriate.

We acknowledge the help of Cora Christmas, Manchester Children's Tumour Registry, and Alice Disbro, Children's Hospital, Columbus Tumour Registry. The Table was prepared by Jillian M Birch.

The Manchester Children's Tumour Registry and United Kingdom Children's Cancer Study Group are funded by the Cancer Research Campaign.

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