

Botryoid Wilms Tumor: a non-existent “entity” causing diagnostic and staging difficulties

INTRODUCTION

Wilms tumor is the most common renal tumor of childhood, representing ~90% of all tumors up to 15 years of age. Patients around the world are treated according to one of the two major protocols, the Children’s Oncology Group (COG, which incorporated the National Wilms Tumor Study Group), in which primary surgery is followed by postoperative chemotherapy and, in indicated cases, radiotherapy, or the International Society of Paediatric Oncology (SIOP), in which treatment includes preoperative chemotherapy followed by chemotherapy and radiotherapy, if necessary¹. The prognosis for patients with Wilms tumor is generally excellent and depends on histological type and stage¹.

In 1981 the term botryoid Wilms tumor was introduced to describe a specific growth pattern of Wilms tumor², and since then numerous cases have been reported claiming it to be a separate subtype of Wilms tumor with better prognosis. However, ‘botryoid Wilms tumor’ is not recognized as a separate type of Wilms tumor in the two major renal tumor study groups, COG and SIOP¹.

The aim of this study was to establish how common this ‘botryoid’ Wilms tumor is, which histological types of Wilms tumor are associated with a botryoid growth pattern, and whether or not ‘botryoid’ Wilms tumor has a better prognosis. Literature was also reviewed to ascertain the clinico-pathological features of published cases of botryoid Wilms tumor.

MATERIALS AND METHOD

Patients

The SIOP UK WT 2001 trial was a United Kingdom (UK) multicentre study which was a part of the SIOP WT 2001 trial, and it registered patients with renal tumors from all pediatric primary cancer treatment centres in the UK and Ireland (841 cases), and in

addition a few patients from centres in New Zealand (6 cases) and Australia (2 cases). Informed consent was provided for all participants.

Inclusion Criteria

This study included the patients who fulfilled the following criteria: a) diagnosed pre- or postoperatively as having intrarenal Wilms tumor; b) had total and/or partial nephrectomy; and c) tumors reviewed by the UK and SIOP Renal Tumor Pathology Panel.

Histological Review

A retrospective analysis of institutional and central pathology reviewer's reports was performed to identify cases in which the term 'botryoid' was mentioned on either gross or histological examination and slides of such cases re-reviewed. All registered cases were sampled according to the SIOP 2001 Trial Pathology protocol³ and submitted for central pathology review for diagnosis, classification and staging³, done by the Children's Cancer and Leukaemia Group Renal Tumor Pathology Panel (chaired by one of the authors, GMV). Each case included a full set of histological slides. Cases were also later reviewed by the SIOP Renal Tumour Pathology Panel. The number of slides submitted varied from 6 to 78 (median 28), with only 3% of cases having fewer than 10 slides. In these cases it was clearly stated that tumors were small and virtually completely sampled. WTs treated with preoperative chemotherapy were classified as low risk (completely necrotic tumors), intermediate risk (epithelial, stromal, mixed, regressive, focal anaplasia types) or high risk (blastemal or diffuse anaplasia type) as per the SIOP WT 2001 Classification⁴. Primarily operated tumors were classified as non-anaplastic and anaplastic Wilms tumors. Where nephrogenic rests were present they were classified as perilobar nephrogenic rests, intralobar nephrogenic rests, both/combined (perilobar and intralobar nephrogenic rests), and multiple nephrogenic rests - nephroblastomatosis.

In addition, a literature search was carried out using descriptive terms of botryoid Wilms tumor, fetal rhabdomyomatous nephroblastoma and teratoid Wilms tumor.

RESULTS

There were 849 patients registered in the Study, and 739 of them were diagnosed with Wilms tumor. Seventy seven (10.3%) patients had Wilms tumor showing botryoid growth pattern (79 tumors because two patients had tumors showing botryoid growth bilaterally). No tumors other than WT in this series showed botryoid growth. Overall there were similar sex distributions (41 males and 36 female (1.1 : 1 ratio)), compared to 304 males and 358 females for non-botryoid cases in the whole UK Wilms tumor group study ($z=1.22$, $P=0.22$)

The median age at presentation for all Wilms tumor patients and those with 'botryoid' Wilms tumor was 39 months (age range for botryoid Wilms tumor was 4 to 172 months).

Only one patient with botryoid Wilms tumor was syndromic (Denys-Drash syndrome) and he presented with bilateral Wilms tumors, only one of which was 'botryoid' Wilms tumor.

In 40 cases Wilms tumor was in the left kidney, in 29 affecting the right kidney, and in one a horseshoe kidney. Bilateral tumors were found in 7/77 (9%) cases, two of which shared botryoid features in both. Two other patients showed botryoid tumors in one kidney and nephrogenic rests accounting for the lesions in the other kidney.

Wilms tumors showing botryoid growth were histologically sub-classified as stromal - 29 (including 17 cases of FRN), mixed - 22; regressive - 7; blastemal - 4; completely necrotic- 3; epithelial -2; diffuse anaplasia - 2; and non-anaplastic (no preoperative-chemotherapy) - 10 cases. In 26/79 (33%) cases tumor extended down the ureter's lumen, but without infiltration of its wall. In one case tumor reached the urinary bladder but, again, without infiltration of its wall. There was a significantly greater proportion of stromal type ($Z=6.64$, $P<0.0001$), and lower proportion of regressive type ($z=-5.2$, $P<0.0001$) tumours in the botryoid cases compared to the overall WT population.

The stage distribution was as follows: stage I - 26 (34%); Stage II - 24 (31%); Stage III - 12 (16%); Stage IV - 9 (12%); Stage V - 6 (8%)(3 sub-stage I; 1 sub-stage II and 2 sub-stage III). In six cases the institutional pathologists assigned tumors as stage 2 because of the botryoid growth alone - they were down-staged to stage 1 on central pathology review.

There were two cases which showed Tamm-Horsfall protein with tiny mature tubules in the sinuses of the lymph nodes – this finding was not taken into account for staging purposes.

Nephrogenic rests were found in 38/79 (48%) cases including intralobar nephrogenic rests in 22 patients (in eight cases the intralobar nephrogenic rests accounted for the botryoid growth itself), perilobar nephrogenic rests in 12 patients, and both intra- and perilobar nephrogenic rests in four cases.

Ten patients underwent primary nephrectomy due to young age, cystic nature of the lesion, sudden bleeding and unknown indication. All other patients (67 in total) underwent tumor biopsy, followed by preoperative chemotherapy (four weeks with two drugs for localized tumors, and six weeks with three drugs for metastatic tumors at presentation), and surgery. Postoperative treatment was given according to tumor's type and stage, as per SIOP WT 2001 protocol. Surgery was radical nephrectomy in 74 cases, in one case it was partial nephrectomy, in one double partial nephrectomy, and in one a resection of the isthmus in a horseshoe kidney was done.

Out of 77 patients, 69 (90%) were alive and well, with no evidence of disease on a long follow up (from 6 years to 15 years). There were 5 (7%) patients who relapsed but after the relapse treatment were alive and well, and 3 (4%) who relapsed and died (Table x). There was no difference in overall outcome between the botryoid and non-botryoid cases ($Z=1.44$, $P=0.15$).

Review of the literature

The extensive retrieval from literature revealed a heterogeneous collection of papers. They included a 50 year timeframe (1968-2017), have different backgrounds (some were written by radiologists, some by surgeons, and some by pathologists), approaches and scopes. In some papers botryoid Wilms tumor growth was mentioned within other tumors, such as fetal rhabdomyomatous nephroblastoma, but cases were not clearly identified, so their features could not be included in the review.

To our knowledge, the term 'botryoid' was used for the first time referring to kidney tumors by Harbaugh in 1968⁵, for a neoplasm growing into the renal pelvis. It showed prominent rhabdomyoblastic differentiation and at that time it was considered to be a sarcoma.

In total, 31 patients were reported from the following countries: USA - 8 cases, Asia (Japan + China + India) - 15, Europe (Ireland + Italy + France) - 4, Turkey - 3, and Morocco - 1 (Table X)⁵⁻³⁵. There were 20 males and 10 females (2:1 ratio) (in one case the gender was not stated). The median age of the reported cases was 24 months (age range from 4 to 108 months). Two Japanese children with Wilms tumor-Aniridia-Growth Restriction (WAGR) syndrome was reported in the literature^{16, 23}.

In 12 cases the tumor was in the left, in 14 in the right, and in five in both kidneys. Histological type of Wilms tumor was not mentioned in all cases, or they were just called classic, triphasic Wilms tumors, but in 11/26 (42%) cases, the presence of rhabdomyoblasts was mentioned, and six cases were labelled as fetal rhabdomyoblastic nephroblastoma. In 12 cases tumor extended into the ureter, and in five cases it reached the bladder. The stage distribution was as follows: stage 1 - two patients, stage 2 - five patients, stage 3 - six patients, and stage 5 - five patients. Nephrogenic rests were reported in eight cases, all intralobar nephrogenic rests, but in four of them the authors were not absolutely certain whether or not they were present. Interestingly, judging by the figures in the paper, in Mahoney et al. case², it is actually intralobar nephrogenic rests that were showing botryoid growth, rather than 'botryoid sarcoma' as it was called in the paper, although the authors considered a possibility of these structures being Wilms 'tumourlets' – the term which in the past was used to describe some types of nephrogenic rests.

The patients received very different treatments, for reasons which were not always obvious from the reports (Table 1). Three patients were treated with preoperative chemotherapy followed by surgery only in one case (stage 5)³³, surgery and chemotherapy in one (bilateral, stage 2)²⁴ and surgery, chemotherapy and radiotherapy (stage 3)²⁹. Twenty patients were treated with primary surgery followed by: no further treatment in one case¹⁴, radiotherapy only in one case (stage 5)³², chemotherapy and radiotherapy in four cases, and

chemotherapy in 14 cases. In one case (no stage given) chemotherapy was given for 12 months²⁴.

Follow up was available in 21/31 cases. One patient died postoperative due to infection. Three patients relapsed and were doing well after further treatment. Seventeen patients were disease free on the follow up varying from six months to 6.5 years.

DISCUSSION

Botryoid is a descriptive term used to describe tumors with a lobular 'grape-like' gross pattern growing in a polypoid fashion into a lumen. Botryoid rhabdomyosarcoma, which refers to such tumors protruding into mucosa-lined hollow organs (such as bladder, uterus/vagina, biliary tree), is a typical example and for a long time it was regarded as a tumor type with superior prognosis, but in the latest WHO classification it was classified with other embryonal rhabdomyosarcomas as a tumor of an intermediate risk³⁶.

Although the term 'botryoid' Wilms tumor was first used by Mahoney *et al.* in 1981², an intrapelvic growth of Wilms tumor was reported previously⁵⁻¹¹, especially in Wilms tumors labeled as fetal rhabdomyomatous nephroblastoma³⁷. However, no paper in the literature attempted to clearly define this alleged type, i.e. to suggest the criteria such as how much of the botryoid growth is required to make the diagnosis – any polypoid growth, exclusively polypoid tumor, or a combination of polypoid and parenchymal tumor. In the COG and SIOP classifications and terminology, the term botryoid Wilms tumor has never been used.

Our study demonstrated that botryoid growth in Wilms tumor is common, occurring in about 10% of cases. Since no other tumor in our series showed botryoid growth, if imaging studies demonstrate a lesion growing in to the real pelvis, it is reasonable to regard it as a Wilms tumor as the first option. Interestingly, the extremely rare, recently described anaplastic sarcoma of the kidney, often grows in a botryoid fashion (in 25% of cases)³⁸.

Some clinico-pathological features such as male to female ratio (reversed in botryoid Wilms tumor in comparison to the whole series) and age at presentation (younger age for botryoid

Wilms tumor) were different between typical Wilms tumors and botryoid Wilms tumor. We found only one case of botryoid Wilms tumor associated with a syndrome (Denys-Drash syndrome), and there have been two further cases in the literature associated with WAGR syndrome^{16,24}.

Unlike fetal rhabdomyomatous nephroblastoma which, allegedly, is bilateral ~30% of cases, and not infrequently shows a botryoid growth (~20% of our and published cases were fetal rhabdomyomatous nephroblastoma), bilateral presentation of botryoid Wilms tumor was not a striking feature in our series or in the literature - 9% and 12%, respectively.

Although the majority of botryoid Wilms tumors treated with preoperative chemotherapy were of stromal type (37% in total, and 72% of them were fetal rhabdomyomatous nephroblastoma), other subtypes were represented, too including mixed (28%) and regressive (9%) types as the most frequent ones. Interestingly, high risk tumors in SIOP Classification, blastemal (5%) and diffuse anaplasia types (3%) were associated with a botryoid growth, too – only one anaplastic botryoid Wilms tumor has been reported before but it was not specified whether it was diffuse or focal anaplasia (29). In our group of WTs treated with primary surgery, 10/25 (40%) of tumors showed botryoid growth, and were histologically classified as non-anaplastic Wilms tumors.

Nephrogenic rests were found in a nearly half of botryoid Wilms tumors, similar to the frequency in the whole SIOP UK WT 2001 Study series³⁹. Since intralobar nephrogenic rests are frequently found in the renal pelvis, it is not surprising that they were found more frequently than perilobar nephrogenic rests in botryoid Wilms tumors, and in 10% of cases they were the only structure showing intra-pelvic, botryoid growth. In the published papers, nephrogenic rests were found in 32% of cases, and in rare cases³¹ they were responsible for a botryoid appearance. Yanai *et al.* suggested that botryoid Wilms tumors originate from these intralobar nephrogenic rests²⁶.

Since postoperative treatment depends on tumor's histological type and stage, it is critical to diagnose and stage tumors accurately, in order to avoid giving a wrong treatment. The staging issue in botryoid Wilms tumor has never been specifically addressed, and not all

published papers mentioned which stage had been assessed and for what reason. In previous reported cases it seemed that the stage 2 assignment was based upon the botryoid growth only, as it was in 8% of cases in our series. In the earlier publications, the botryoid growth has been referred as "rupture into the collecting system"^{10,19}. This is misleading because a WT growing in a botryoid fashion is usually not infiltrating the pelvic wall, so intrapelvic botryoid growth should not be regarded as renal sinus / pelvic invasion, and a criterion / reason for upstaging a tumor. Even when tumor extends into the ureter and reaches the bladder without infiltrating the wall, as it was in one-third of our cases, and in over 50% of reported cases, it should still be regarded as stage 1. Genuine infiltration of the ureter wall is a rare event and has not been recorded in the NWTs study (0/45 cases)⁴⁰. It is important to be aware of this growth when planning surgery. Distal ureteral and vesical relapses were reported in the past but they are prevented by early ligation of the distal ureter before the tumor is manipulated^{6,9,25,41}.

An interesting finding in our series is the presence of small tubules accompanying Tamm-Horsfall protein in the lymph nodes sinuses, found in nearly 10% of cases. Botryoid tumors are associated with ectatic sinus vessels containing Tamm-Horsfall protein, probably due to the obstructive effect of the polypoid mass (hydronephrosis is a common feature in these patients), and one should be aware of this phenomenon and not upstage such cases as positive lymph nodes⁴².

The differential diagnosis between nephrogenic rests and versus Wilms tumor is particularly difficult in pure botryoid lesions without any parenchymal involvement. Intralobar nephrogenic rests were regarded as the only component of a botryoid growth in ~10% of our cases. There is clearly a continuum between nephrogenic rests and WTs, and it must be said that stringent, widely-accepted and reproducible criteria have not been provided yet and this distinction still relies upon subjective, more experience-based than evidence-based criteria.

In the published cases, primary surgery was performed in 19/24 (80%) cases, but only in 13% of our cases, reflecting the two mentioned approaches used in the countries where the cases were coming from. While children in our Study were treated according to the SIOP WT

2001 Trial and Study Protocol for pre-treated or primarily operated tumors, treatment given in published varied significantly. Still, the outcomes were similar: the event free survival in our series was ~90%, and the overall survival as high as 96%. In the published cases, the event free survival was lower (86%), but the overall survival as good as in our series, and the only fetal outcome was recorded in a patient who died postoperatively of pneumonia.

CONCLUSIONS

Botryoid Wilms tumor does not represent distinct 'entity' and has no distinguishing clinicopathological features. WT showing this growth pattern should be classified on the basis of their overall histological features. The term botryoid WT is a descriptive term that should not be used in the final diagnosis since it has no clinical or prognostic significance. It is a relatively common finding (found in ~10% of Wilms' tumors in our large series) and with the 'spectrum' of WT sub-types (from completely necrotic to diffuse anaplasia). Staging assignment of these tumors maybe difficult as some assume that intrapelvic, botryoid is evidence of tumor's invasion in the renal pelvis. The prognosis of these tumors depends on tumor's histological subtype and stage, rather than on the presence of botryoid growth.

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We report a case of botryoid Wilms' tumor that occupied the renal pelvis and extended into the bladder. A 3-year-old boy was referred to us with a chief complaint of gross hematuria and micturition pain. Computed tomography showed tumor occupying the right renal pelvis and ureter and extending into the bladder. Right radical nephroureterectomy was performed. The resected specimen showed a botryoid sarcoma-like appearance, occupied the right renal pelvis and ureter, and protruded into the bladder. Histologic findings showed typical triphasic Wilms' tumor. Botryoid Wilms' tumor has been reported in only 16 cases in the literature and in only 3 cases extended into the bladder.