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The Germinal Triumvirate- Wilm's Tumour

Anubha Bajaj*

[1]*Consultant Histopathology, A.B. Diagnostics, New Delhi, India.*

***Corresponding author:**
Anubha Bajaj, Consultant Histopathology, A.B. Diagnostics, New Delhi, India.

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Wilm's tumour is a malignant, paediatric neoplasm originating from nephrogenic blastema which simulates developing renal parenchyma.

Additionally, designated as nephroblastoma, tri-phasic embryonal Wilma's tumour is constituted of varying quantities of blastemal, epithelial and stromal components. Besides, biphasic and monophasic neoplasms are frequently discerned. Epithelial and stromal elements may emerge as poorly differentiated to well differentiated components. Morphological assessment of tri-phasic Wilm's tumour is efficacious and confirmatory. However, appropriate categorization of neoplasms composed of pure blastema, epithelium or stroma can be challenging. Extensive tissue sampling, pertinent immunohistochemistry and molecular techniques are advantageously adopted in discerning cogent diagnostic features.

Tumefaction is commonly discerned within ~ 4 years. Adults are infrequently incriminated. A mild female preponderance is observed. Majority of neoplasms are non-syndromic whereas ~15% Wilm's tumour are associated with specific syndromes and congenital anomalies. Familial instances may occur [1,2].
Wilm's tumour preponderantly incriminates renal parenchyma. Congenital or extra-renal neoplasms are extremely exceptional. Around ~10% tumefaction are bilateral [1,2].

Of obscure pathogenesis, nephrogenic rests emerge as precursor lesions of unilateral and bilateral Wilm's tumour. Generally, peri-lobar and intra-lobar nephrogenic rests are delineated [1,2]. Discernible peri-lobar nephrogenic rests in children <one year enunciates a predominantly enhanced possible emergence of Wilm's tumour within contralateral kidney [1,2]. Wilm's tumour exemplifies significant genetic alterations within WT1 (chromosome 11p13), CTNNB1 (chromosome 3p22), IGF2 (chromosome11p15), TP53 (chromosome 17p13), MYCN (chromosome 2p24) or chromosomal 1q gain.

Wilm's tumour is posited to arise from persistent metanephric tissue or nephrogenic rests. Genetic alterations may concur with embryogenesis of genitourinary tract [1,2]. Tumorigenesis is associated with WT1 gene at chromosome 11p13, WT2 gene at chromosome 11p15 and associated, unidentified genetic modifications [1,2].

Wilm's tumour manifests as an abdominal tumefaction devoid of cogent clinical symptoms. However, associated symptoms as abdominal pain, haematuria, hypertension or anaemia may ensue [1,2]. Commonly discerned predisposition syndromes appear as •high risk group demonstrating Wilms tumour - aniridia - genitourinary anomalies - intellectual disability(WAGR) or Denys-Drash syndrome. •moderate risk group depicting Beckwith Wiedemann syndrome, Simpson-Golabi-Behmel syndrome or Frasier syndrome. •low risk group delineating Bloom's syndrome, DICER1 syndrome, Li-Fraumeni syndrome or isolated hemi-hypertrophy ([1,2].

Grossly, an enlarged, solitary or multinodular, spherical, lobulated, soft, friable, well demarcated tumefaction is discerned within renal parenchyma along with distorted renal outline [1,2]. Cystic countenance may be predominant. Neoplasms subjected to therapy exhibit focal or extensive necrosis and haemorrhage. Renal sinus with vascular articulations and ureter requires evaluation.

As per Children's oncology group (COG), histological classification of Wilm's tumour is comprised of anaplastic (unfavourable) and non-anaplastic (favourable) neoplasms [1,2]. Upon microscopy, Wilm's tumour is characteristically comprised of distinctive components as blastema, epithelium and stroma. Neoplasms constituted of singular or dual components are commonly discerned. •blastemal component is minimally differentiated and exhibits miniature to medium-sized undifferentiated cells incorporated with uniform, miniature nuclei and tiny nucleoli. Mitotic figures are frequently delineated [1,2]. Blastema may articulate distinctive patterns as diffuse, serpentine, nodular or basaloid, configurations which are devoid of prognostic significance [1,2].

Epithelial component enunciates poorly differentiated, rosette-like configurations, moderately differentiated tubules or papillary articulations or well differentiated glomerular-like structures and

miniature, mature tubules. Heterologous epithelial elements as squamous epithelium, mucinous epithelium or glial tissue may appear [1,2]. Stromal component may emerge as hypo-cellular or hyper-cellular and manifests as undifferentiated areas or well differentiated areas. Tumour cells display indistinct cellular outline, elliptical to spindle-shaped nuclei and bland nucleoli. Heterologous tissue elements as rhabdomyoblasts, adipose tissue or mature cartilage can be discerned [1,2]. Anaplasia is a feature denominated with enlarged, atypical, tri-polar or multipolar mitotic figures, prominent nuclear enlargement and hyperchromatic nuclei. Blastema, epithelium or stroma may demonstrate anaplastic features [1,2]. Focal anaplasia exhibits a clearly defined focus of nuclear modifications confined to primary intrarenal tumour. As per Children's oncology group (COG), focal anaplasia enunciates ~4 miniature foci of anaplastic cells. Alternatively, International society of paediatric oncology (SIOP) designates focal anaplasia as up to 2 foci anaplastic cells of ~ 15-millimetre magnitude [1,2]. Diffuse anaplasia exemplifies non-localized anaplasia or focal anaplasia intermingled with prominent nuclear unrest within diverse regions or anaplasia extending beyond tumour capsule or anaplastic cells invading intrarenal or extra-renal blood vessels, renal sinus, extracapsular sites, distant metastatic sites or anaplasia discerned within surgical tissue sample [1,2].

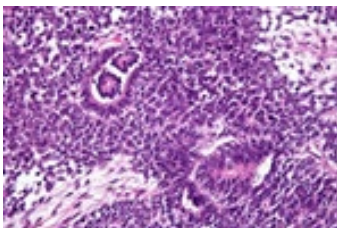

Figure 1: Nephroblastoma comprised of tri-phasic blastema, epithelium and stroma with configuration of glandular structures and small round undifferentiated cells(5).

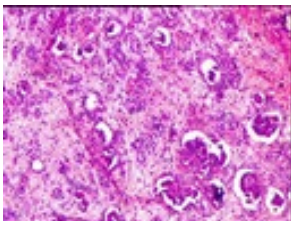

Figure 2: Nephroblastoma configured of blastema, epithelium and stroma with immature nephrons(6).

Staging of Wilm's tumour as per Children's oncology group is denominated as •stage I demonstrating neoplasm confined to unilateral kidney which can be comprehensively eradicated with surgical excision. Renal capsule is intact. Vascular or peri-renal tumour infiltration is absent. Pre-operative surgical tissue sampling is unaccomplished. •stage II where tumour is confined to unilateral kidney with dissemination into peri-renal adipose tissue, soft tissue, vascular articulations and renal sinus. Tumefaction can be alleviated with comprehensive surgical extermination. Regional lymph node metastasis is absent. Pre-operative surgical tissue sampling is unaccomplished. •stage III where tumour is intra-abdominal and disseminates into peri-renal tissues, adjacent organs, vascular articulations, peritoneal implants, excised surgical tissue perimeter or regional lymph nodes. Tumour 'spill' into peritoneal cavity preceding or during surgical intervention may ensue. Tumour eradication with surgical excision remains incomplete and tumefaction may be extracted in >one piece. Metastasis into intra-thoracic or distant lymph node groups is absent. Pre-operative surgical tissue sampling is accomplished. •stage IV where distant metastasis into viscera as lungs, liver, brain, bone or distant lymph nodes may occur. •stage V where tumour incriminates bilateral renal parenchyma. Staging of individual tumour within singular renal parenchyma is required •refractory Wilm's tumour is constituted of a neoplasm which lacks decimation during or subsequent to therapy. •recurrent Wilm's tumour is a neoplasm which reappears following initiation of cogent therapy. Site of neoplastic recurrence may be identical to or diverse from site of initial tumour emergence. Reappearing Wilm's tumour requires evaluating and staging procedures akin to initial primary tumour [3,4].

Wilm's tumour is immune reactive to WT1, INI1 or glypican 3. Blastema is diffusely immune reactive to WT1, PAX8, vimentin, variably immune reactive to CD56, CD57, cytokeratin, EMA or desmin and exceptionally immune reactive to cyclin D1 [3,4]. Epithelium is immune reactive to cytokeratin, EMA, CD56, variably immune reactive to PAX8, WT1 and focally immune reactive to cyclin D1 [3,4]. Stroma is immune reactive to vimentin, variably immune reactive to BCL2 or CD34 whereas minimal or absent immune reactivity to WTI is observed [3,4]. Heterologous skeletal muscle component is immune reactive to desmin, myogenin or Myo D1(3,4). Wilm's tumour is immune non-reactive to AMACR, CK7, Melan A, HMB45, BRAF V600E, TFE3, TFEB, BCOR or FLI1[3,4].

Wilm's tumour composed of pure blastemal component requires segregation from rhabdoid renal tumour, neuroblastoma, Ewing's sarcoma or desmoplastic small round cell tumour [3,4]. Wilm's tumour composed of pure epithelial component necessitates segregation from hyperplastic peri-lobar nephrogenic rests, papillary renal cell carcinoma or metanephric adenoma [3,4]. Wilm's tumour comprised of pure stroma mandates demarcation from clear cell renal cell carcinoma, congenital mesoblastic nephroma or metanephric stromal tumour [3,4]. Additionally, exceptional neoplasms as synovial sarcoma, renal medullary carcinoma, inflammatory myofibroblastic tumour or renal cell carcinoma with sarcomatous differentiation require distinction. Wilm's tumour can be appropriately discerned with cogent imaging techniques. Plain radiography of thoracic cavity, ultrasonography or magnetic resonance imaging of abdomen and computerized tomography of abdomen and thoracic cavity is optimally recommended. MRI diffusion studies may aid segregation of Wilm's tumour from neuroblastoma [3,4].

Complete blood count, renal function tests and coagulation assay requires assessment along with catecholamine levels to exclude

neuroblastoma [3,4].

Therapeutic strategy of Wilm's tumour is multimodal and comprised of surgical intervention combined with chemotherapy or radiotherapy, manoeuvers which are applicable in advance stage neoplasms. International society of paediatric oncology (SIOP) recommends employment of neoadjuvant chemotherapy for subjects > 6 months followed by surgical excision. Low risk, stage I Wilm's tumours do not require additional therapy. Advanced stage neoplasms mandate adjuvant chemotherapy and radiotherapy. Focal anaplasia is an intermediate risk factor whereas diffuse anaplasia and blastemal subtype are classified as high-risk factors [3,4]. Children's oncology group (COG) recommends surgical extermination of low risk, non-anaplastic, stage 1 tumours occurring in subjects <2 years with absent regional lymph node metastasis, absent loss of heterozygosity (LOH) within chromosome 1p and 16q and neoplastic weight < 550 grams [3,4]. Contingent to histology, tumour stage and molecular characterization, Wilm's tumour lacking aforesaid categorization or advanced stage neoplasms can be subjected to preliminary surgical extermination, chemotherapy and radiotherapy [3,4].

Tumour histology and disease stage are significant prognostic factors. Prognostic outcomes may be defined with factors such as age, weight of neoplasm, rapidity of therapeutic response to pulmonary nodule or discernible molecular markers as loss of heterozygosity at chromosome 1p and 16q. Chromosomal gain at 1q is accompanied by inferior outcomes [3,4]. Prognostic outcomes of Wilm's tumour are contingent to •neoplastic morphology wherein a favourable histological countenance is accompanied by superior prognosis. Anaplastic, rapidly progressive tumours occurring in adolescents necessitate aggressive treatment strategies and are minimally responsive to chemotherapy or radiation therapy [3,4]. •tumour stage where stage I or stage II neoplasms are amenable to therapy. Anaplastic tumours of advanced stage demonstrate decimated response to diverse therapeutic measures. Tumour staging is singular and identical in morphologically diverse neoplasms, irrespective to histological components [3,4]. Discernible prognostic outcomes are contingent to •cogent risk stratification into low risk, intermediate risk and high-risk groups. •tumour volume with or without adoption of neoadjuvant chemotherapy. •therapeutic response of pulmonary metastases to initial chemotherapy. Currently, Wilm's tumour exhibits an overall survival of ~ 90%. Tumour relapse may occur predominantly within 2 years of initial tumour discernment [3,4].

Table 1: Risk stratification of Wilm's tumour (COG)

Low risk	Cystic, partially differentiated nephroblastoma
Intermediate risk	Tumefaction with favourable histology. Absence of anaplasia
High risk	Focal anaplasia/ Diffuse anaplasia

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