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Interstitial Cells of Cajal in Pelvi-Ureteric Junction Obstruction: Diagnostic and Reporting Considerations for Surgical Pathologists

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Dear Editor,

Pelvi-ureteric junction (PUJ) obstruction is a frequent cause of paediatric hydronephrosis, yet its histopathological evaluation often yields limited explanatory value beyond exclusion of overt fibrosis or inflammation (1). In recent years, attention has shifted toward interstitial cells of Cajal (ICCs) as potential contributors to functional obstruction at the PUJ. However, from a diagnostic pathology perspective, the assessment and interpretation of ICCs remain fraught with methodological and conceptual challenges, which merit critical appraisal.

ICCs serve as pacemaker cells regulating coordinated ureteral peristalsis and several studies have demonstrated reduced ICC density and disrupted spatial organization in resected PUJ segments from children with obstruction compared with controls (1,2). Importantly, such alterations are often identified in specimens lacking significant fibrosis, inflammation, or fixed luminal narrowing, supporting a neuromuscular basis for obstruction. While biologically plausible, translation of this concept into routine diagnostic practice is hindered by the absence of standardized evaluation criteria. Foremost among these is age-related variability (1-3). ICCs undergo postnatal maturation, with increasing density and network complexity during early childhood. Consequently, ICC counts that may be physiologically appropriate in infants could represent a true pathological reduction in older children. Reduced ICC counts in a 4- to 6-year-old child are more likely to be pathological than developmental, whereas similar findings in infants may fall within physiological limits. Despite this, most published studies lack robust age-stratified reference data, limiting their applicability to individual cases. Another important consideration during microscopic assessment of ICCs is the precise site of biopsy, especially in cases of severe obstruction, as investigators have reported differential density of ICC in regions above the PUJ, at the PUJ, and below the PUJ (3,4).

Technical issues further complicate assessment. ICCs are typically highlighted using c-Kit (CD117) immunohistochemistry, but mast cells, which also express CD117, are abundant in the ureteric wall and represent a major interpretative pitfall (Figure 1A-D). Importantly, this diagnostic pitfall of CD117+ mast cells may persist even in specimens showing secondary tissue remodeling or mild fibrosis and should not be interpreted as evidence against a functional neuromuscular contribution to the obstruction. Without careful morphological correlation, mast cells may be erroneously included in ICC counts, leading to overestimation. Accurate identification, therefore, requires strict morphological correlation, limiting counts to spindle-shaped intermuscular cells with cytoplasmic processes and avoiding reliance on staining alone. DOG1, which shows cytoplasmic and membranous positivity in gastrointestinal ICCs, has been proposed as an adjunct marker, but its role in routine PUJ diagnostics remains limited (5). Equally important is the lack of standardized reporting criteria. Absolute ICC counts per high-power field, though commonly used in research, lack validated diagnostic cut-offs. In routine practice, a semi-quantitative approach that assesses ICC density (preserved vs reduced), distribution (uniform vs patchy), and continuity (intact vs disrupted networks), is more reproducible and functionally meaningful. ICC findings on immunohistochemistry should not be interpreted in isolation. Smooth muscle architecture, neural elements, and fibrosis must be evaluated concurrently to avoid attributing obstruction solely to ICC paucity. From a diagnostic stand-

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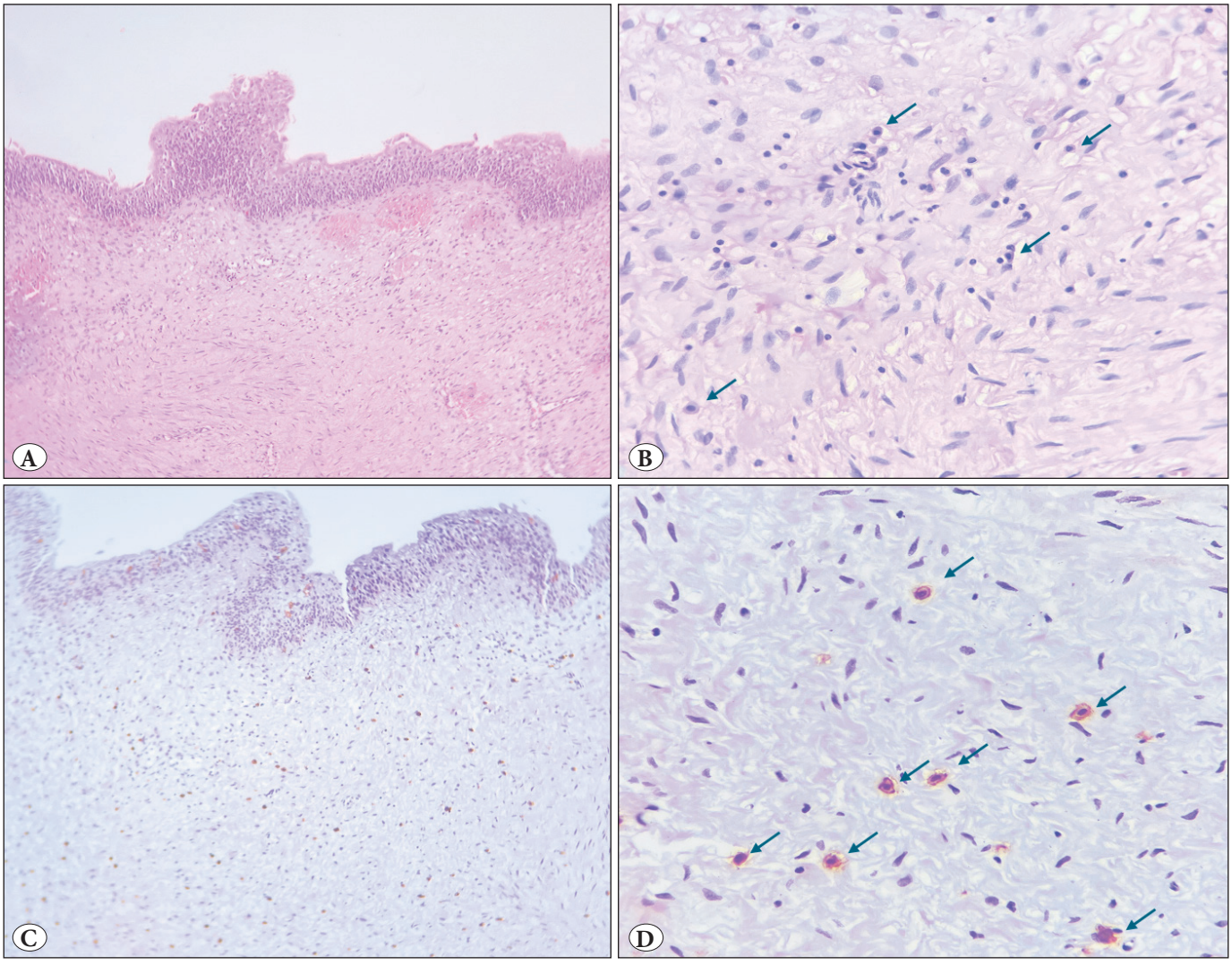


Figure 1: Histopathological and immunohistochemical features in the pelvi-ureteric junction (PUJ) biopsy from a 5-year old child with unilateral hydronephrosis: **(A)** Hematoxylin and eosin–stained section of the PUJ showing urothelium and underlying lamina propria with mild fibrosis (x40); **(B)** High-power view (x400) highlighting mast cells within the stroma (arrows); **(C)** CD117 immunohistochemistry demonstrating scattered positive cells in the PUJ region at low power (x40); **(D)** At higher magnification (x400), it is evident that the CD117-positive cells are mast cells (arrows) instead of interstitial cells of Cajal, which were very sparse in the biopsy.

point, ICC assessment should be regarded as supportive evidence that may explain functional obstruction, rather than a standalone criterion for PUJ obstruction (Figure 2).

In conclusion, ICC evaluation offers valuable insight into the functional pathology of PUJ obstruction but currently occupies a supplementary role in diagnostic histopathology. Adoption of age-aware interpretation, careful morphological validation, and standardized semi-quantitative reporting would enhance consistency and clinical relevance. Future multicentric studies aimed at defining age-matched reference patterns and reproducible scoring systems are necessary before ICC assessment can be fully integrated into routine PUJ pathology reporting.

Conflict of Interest
The author declares no conflict of interest.

Authorship Contributions
Concept: **SP,** Design: **SP,** Data collection or processing: **SP,** Analysis or Interpretation: **SP,** Literature search: **SP,** Writing: **SP,** Approval: **SP.**

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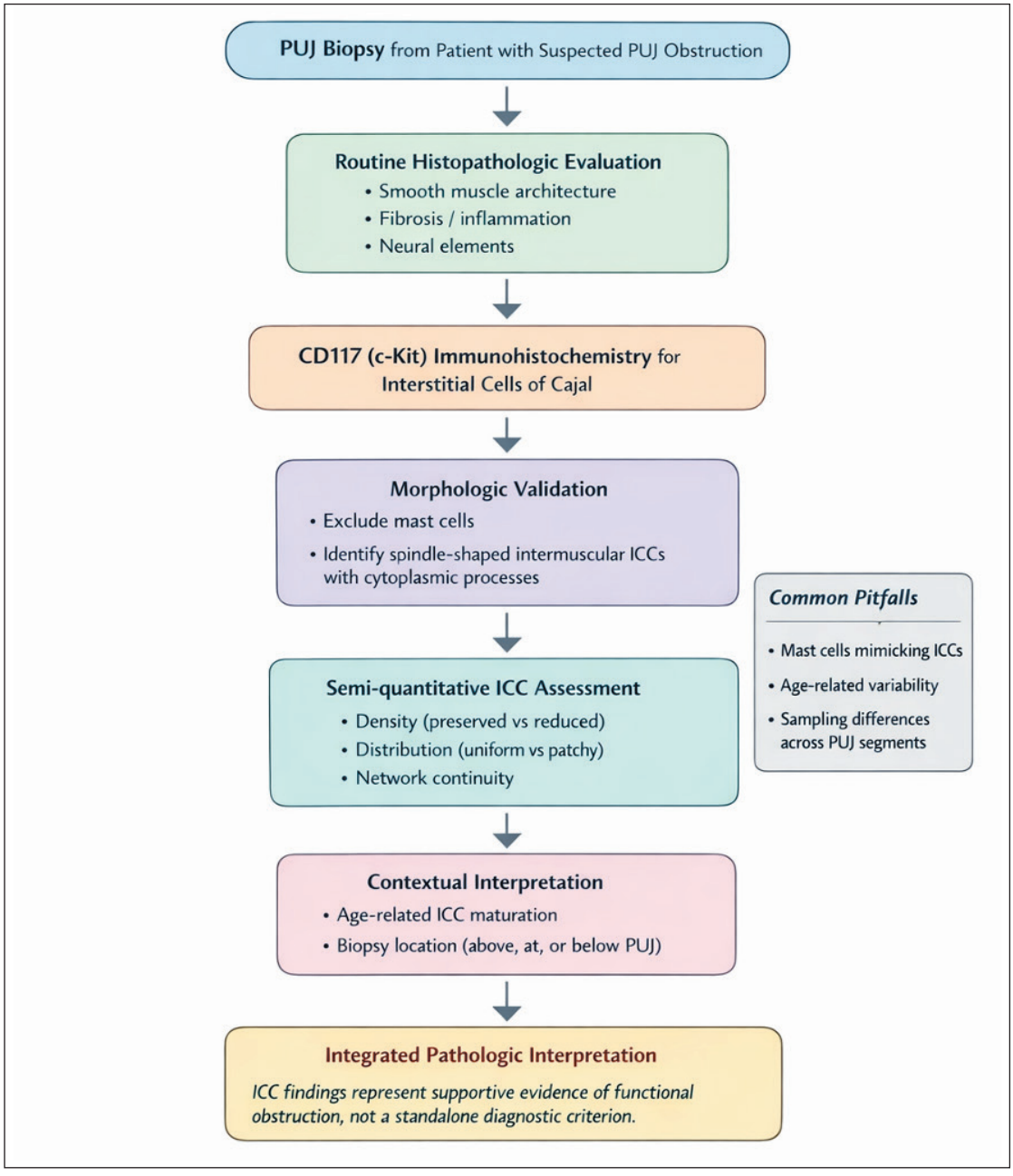


Figure 2: Interpretative framework for assessing interstitial cells of Cajal (ICC) in pelvi-ureteric junction (PUJ) obstruction

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