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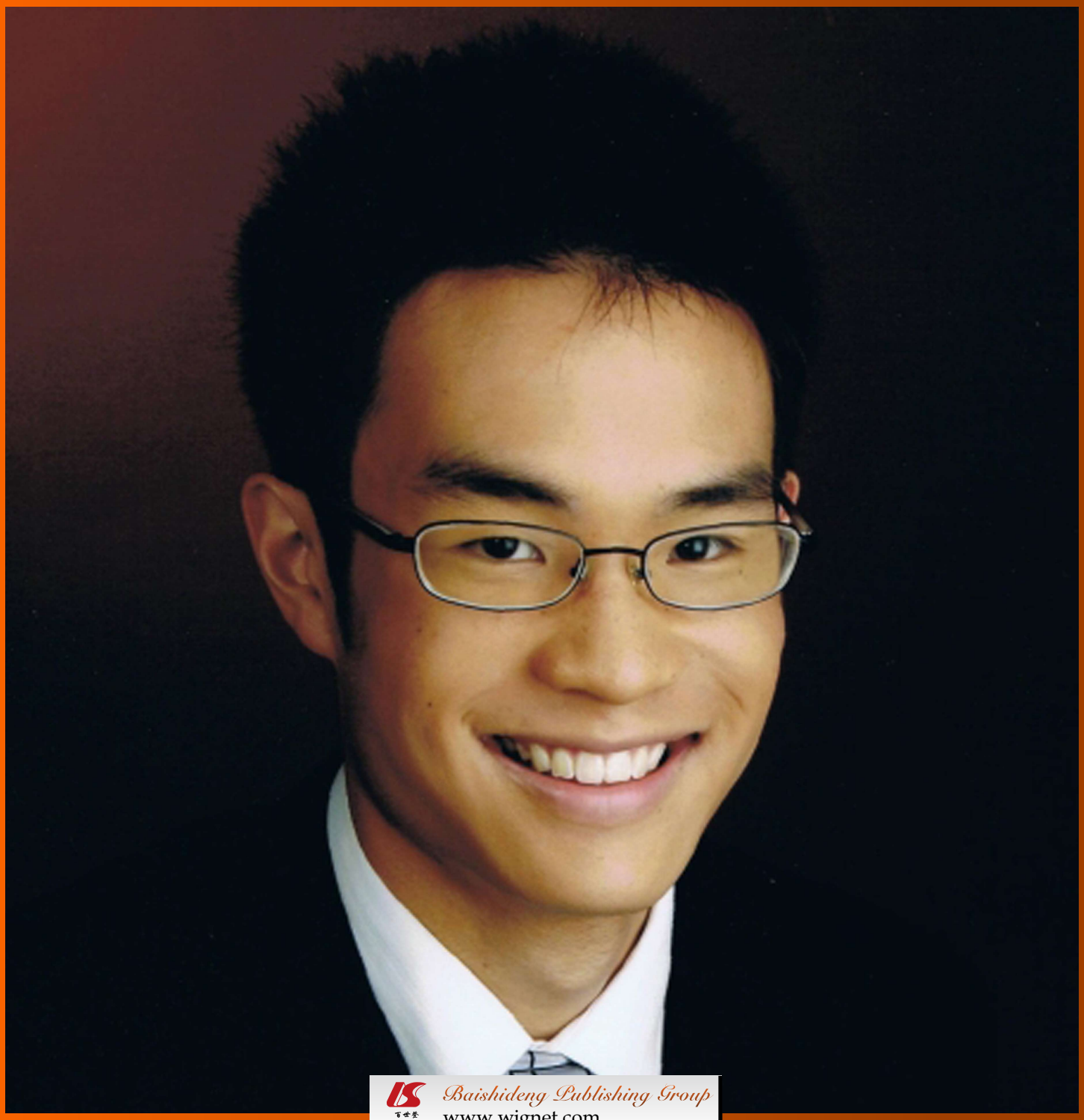

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REVIEW

Renal cell carcinoma: Evolving and emerging subtypes

Suzanne M Crumley, Mukul Divatia, Luan Truong, Steven Shen, Alberto G Ayala, Jae Y Ro

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Abstract

Our knowledge of renal cell carcinoma (RCC) is rapidly expanding. For those who diagnose and treat RCC, it is important to understand the new developments. In recent years, many new renal tumors have been described and defined, and our understanding of the biology and clinical correlates of these tumors is changing. Evolving concepts in Xp11 translocation carcinoma, mucinous tubular and spindle cell carcinoma, multilocular cystic clear cell RCC, and carcinoma associated with neuroblastoma are addressed within this review. Tubulocystic carcinoma, thyroid-like follicular carcinoma of kidney, acquired cystic disease-associated RCC, and clear cell papillary RCC are also described. Finally, candidate entities, including RCC with t(6;11) translocation, hybrid oncocytoma/chromophobe RCC, hereditary leiomyomatosis and RCC syndrome, and renal angiomyoadenomatous tumor are reviewed. Knowledge of these new entities is important for diagnosis, treatment and subsequent prognosis. This review provides a targeted summary of new developments in RCC.

Key words: Renal cell carcinoma; Subtypes; Xp11 translocation; Mucinous tubular and spindle cell; Multilocular cystic clear cell; Carcinoma associated with neuroblastoma recently described entities; Clear cell papillary renal cell carcinoma; Acquired cystic kidney disease; Hereditary leiomyomatosis; Candidate entities; Renal cell carcinoma with t(6;11) translocation

Core tip: New concepts in selected renal cell carcinoma (RCC) subtypes are reviewed. We describe evolving concepts in Xp11 translocation carcinoma, mucinous tubular and spindle cell carcinoma, multilocular cystic clear cell RCC, and carcinoma associated with neuroblastoma. Additionally, tubulocystic carcinoma, thyroid-like follicular carcinoma of kidney, acquired cystic disease-associated RCC, and clear cell papillary RCC are described. Finally, candidate entities, including RCC with t(6;11) translocation, hybrid oncocytoma/chromophobe RCC, hereditary leiomyomatosis and RCC syndrome, and renal angiomyoadenomatous tumor are discussed. This review provides a targeted summary of recent updates for those who diagnose and treat renal cancer.

Crumley SM, Divatia M, Truong L, Shen S, Ayala AG, Ro JY. Renal cell carcinoma: Evolving and emerging subtypes. *World J Clin Cases* 2013; 1(9): 262-275 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i9/262.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i9.262

INTRODUCTION

Many new discoveries have been made with regards to renal cell carcinoma (RCC) in recent years. At the recent meeting of the International Society of Urologic Pathology, the newly defined, recently described, and candidate entities within RCC were discussed. An understanding of these new subtypes is essential for the surgical

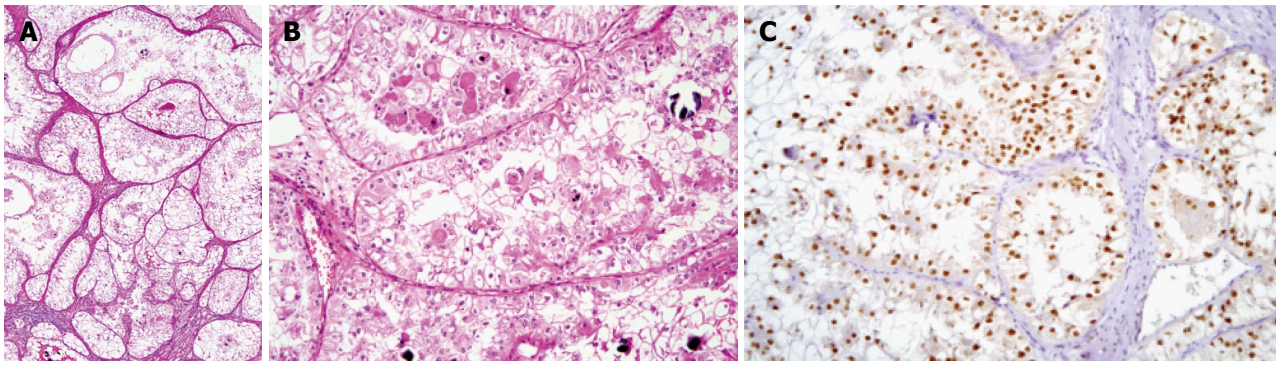

Figure 1 Xp11 translocation carcinoma (hematoxylin and eosin). A: The tumor is composed of cells with clear to eosinophilic, abundant voluminous cytoplasm (× 40); B: Psammoma bodies in stromal hyaline nodules are frequently seen, but are not required for diagnosis (× 100); C: TFE3 nuclear immunohistochemical stain can assist with confirmation of the diagnosis (× 100), but can also be positive in tumors without the molecular translocation.

pathologist and urologist. An awareness of the current knowledge among these physicians will enable effective communication for proper diagnosis, prognosis, and treatment.

The five traditional and well-defined subtypes of RCC (conventional clear cell, papillary, chromophobe, collecting duct, and unclassified) comprise the overwhelming majority of RCC, but will not be discussed in detail here. In this review, we discuss three categories of evolving and emerging entities of renal tumors. The first category includes the newly defined RCC subtypes, the second includes recently described entities and the final category includes candidate entities for RCC subtypes (Table 1). The category of recently described tumors includes neoplasms with accruing evidence that they should be considered independent subtypes. The category of candidate entities includes both renal carcinomas seen in familial cancer syndromes and neoplasms on which there is still speculation to whether they deserve designation as distinct entities. The tumors within all three categories have received much scrutiny in recent years with important updates.

Table 1 Renal cell carcinoma subtypes

Renal cell carcinoma	
Newly defined subtypes	Xp11 Translocation RCC
	Mucinous tubular and spindle cell carcinoma
	Multilocular cystic clear cell RCC
	Carcinoma associated with Neuroblastoma
Recently described entities	Tubulocystic carcinoma
	Thyroid-like follicular carcinoma of kidney
	Acquired cystic kidney disease-associated RCC
	Clear cell papillary RCC
Candidate entities	RCC with t(6;11) translocation
	Hybrid oncocytoma/chromophobe RCC
	Hereditary leiomyomatosis and RCC syndrome
	Renal angiomyoadenomatous tumor

RCC: Renal cell carcinoma.

NEWLY DEFINED RCC SUBTYPES

Xp11 translocation carcinoma

Xp11 translocation RCC was first established by the World Health Organization (WHO) as an independent subtype in 2004[1]. This tumor is defined by a translocation involving the *TFE3* gene with various gene partners, the most common of which are *ASPL* and *PRCC*. The name Xp11 translocation RCC comes from the chromosomal location of the *TFE3* gene (specifically Xp11.2). The tumor is defined by both papillary and clear cell morphology. These tumors can also have a nested architecture, and the type (location) of gene translocation may be reflected in the tumor morphology. *ASPL-TFE3* translocation carcinomas have more abundant cytoplasm and frequent psammoma bodies, while *PRCC-TFE3* translocations have less cytoplasm, less frequent psammoma bodies, and closely nested tumor cells[2]. In general, these tumors have voluminous, clear to eosinophilic cytoplasm, and well-defined cell borders[2-4] (Figure 1). Cystic change, psammoma bodies, spindle cells, giant cells, and biphasic appearance have been described[5,6]. Grossly, they appear similar to clear cell RCC. Xp11 translocation RCC has traditionally been described as occurring more frequently in young adults and children. Recent reports speculate whether these carcinomas may be associated with chemotherapy[7].

These tumors are typically negative for cytokeratin and positive for CD10, RCC marker, vimentin, PAX2, and PAX8[3-5]. A strongly positive nuclear stain for the C-terminal of the *TFE3* gene product is indicative of Xp11 translocation RCC. However, recently, some have questioned the specificity of the TFE3 staining. A recent series by Klatte *et al*[8] examined 848 patients over a 20-year period and found 75 RCCs with features morphologically consistent with Xp11 translocation RCC or occurring in patients 40 years or younger. Of these 75 tumors, 17 (23%) tumors had strong nuclear TFE3 expression. However, only two of these cases had a translocation detected by FISH, yielding a dismal positive predictive value of 12%. This study suggests that the TFE3 immunohistochemical stain can also stain non-translocated *TFE3* product. The average age of patients with RCC positive for TFE3 immunohistochemical staining in this study was 33.4 years. Interestingly, this study also found that strong TFE3 expression in both non-translocated and translocated tu-

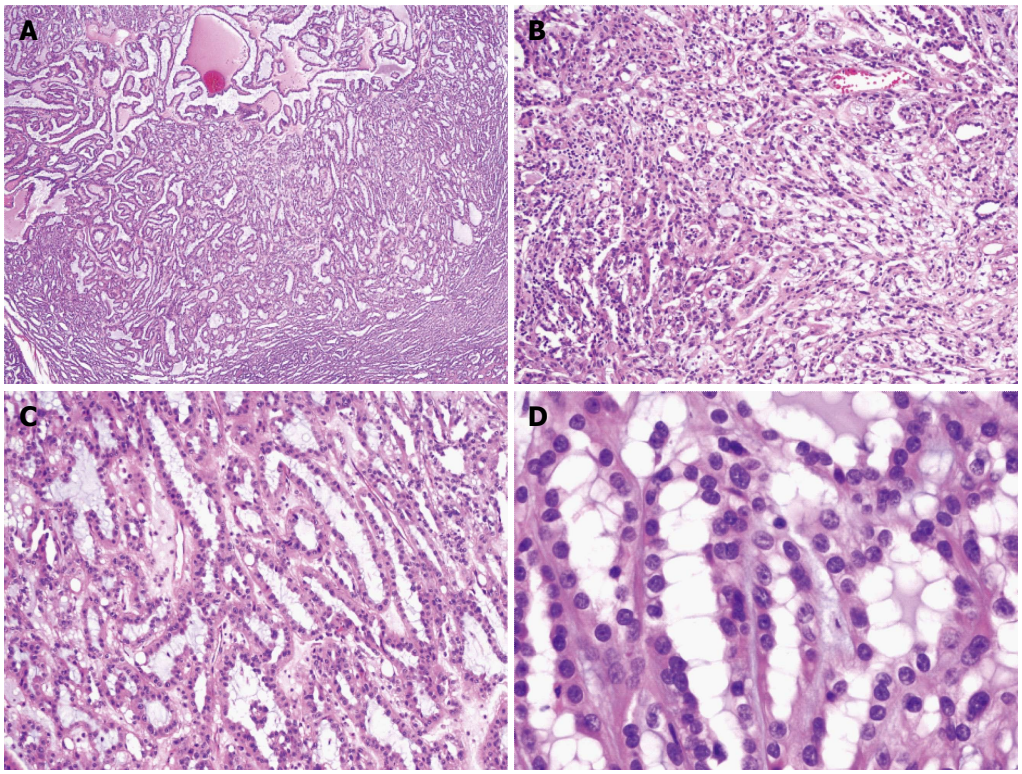

Figure 2 Mucinous and tubular spindle cell carcinoma (hematoxylin and eosin). A: The tumor has a tubular pattern on low power with mucin present between glands (× 20); B: In some areas, a spindle cell pattern is also seen (× 40); C: The tubular pattern with intervening mucin is prominent in some tumors (× 100); D: Round nuclei with prominent nucleoli are evident on higher power (× 400).

mors was associated with larger tumor size, lymph node involvement, and metastasis[8]. Positive TFE3 staining was also associated with worse survival in univariate analysis ($P = 0.032$), albeit this was not significant in multivariate analysis ($P = 0.404$). This evidence suggests that strong TFE3 immunohistochemical staining in adults may be informative for prognosis as well as diagnosis.

Traditionally, Xp11 translocation carcinoma is described primarily in children and young adults. However, recent studies have suggested the presence of these tumors in adults may go unrecognized. A recent study by Zhong *et al*[9] of 121 consecutive RCCs from 2001-2009 in adults at one institution found 6 tumors with Xp11 translocation for a frequency of 5%[9]. While in pediatric RCC, Xp11 translocation RCC has been found in up to one third of all tumors[3], RCC, in general, is much more frequent in adults than in children. Therefore, the majority of Xp11 translocation RCC may occur in the adult population. Additionally, in adults, these tumors may behave more aggressively and have an association with the female gender. Xp11 translocation RCC in adults has been found to present with advanced stage, lymph node metastases, and have a poor survival rate[5]. A recent commentary by Klaassen *et al*[10] in the *Journal of Urology* suggests that adult patients with Xp11 translocation RCC should be classified as high risk for metastasis. They suggest these patients should follow a vigilant surveillance protocol, which includes lifelong follow-up after diagnosis[10].

The differential diagnosis for Xp11 translocation RCC includes clear cell RCC, clear cell papillary RCC, papillary RCC (especially type 2), and the closely related translocation 6;11 carcinoma (discussed below). The *TFE3* translocation is diagnostic for tumors with overlapping morphology. The diagnosis of Xp11 translocation RCC should be investigated in children and young-to-middle-aged adults with characteristic histology that is negative for cytokeratins[9]. New evidence suggests that if the classic morphology is present, the diagnosis should also be considered in adults. Based on these clinicopathologic features, we recommend a cytokeratin stain using a broad spectrum antibody in all RCCs diagnosed before the age of 30. If the cytokeratin is negative or weakly and focally positive, then proceed with a TFE3 stain and/or translocation study to confirm the diagnosis. A translocation carcinoma should be suspected in adults when papillary or nested pattern carcinoma, containing very voluminous clear to eosinophilic tumor cells (with or without psammoma bodies), are present, usually within hyaline stromal nodules. We recommend doing a similar battery of immunostains for RCCs of young adults and children.

Mucinous tubular and spindle cell carcinoma

Mucinous tubular and spindle cell carcinoma (MTSCC) is a fairly newly described tumor which is included in the 2004 WHO classification[11]. This is a tumor defined by the presence of three histologic components: mucin, tumor cells forming tubules, and spindle cells, herein earning its appropriately descriptive name (Figure 2). This tumor occurs throughout life (age range 17-82 years) and is more

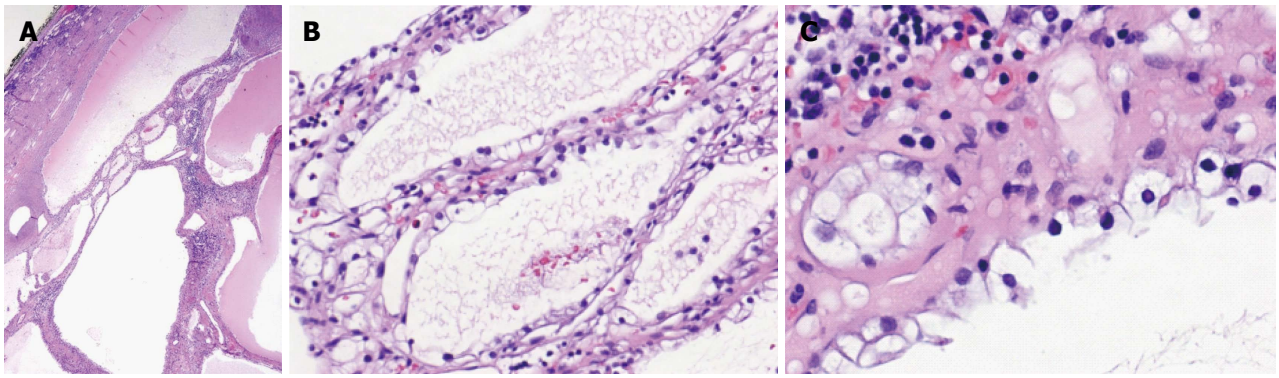

Figure 3 Multilocular cystic clear cell renal cell carcinoma (hematoxylin and eosin). A: The tumor is composed of multiple cysts with intervening thin, fibrous septa and scattered chronic inflammatory cells (× 40); B: On higher power, the cysts are lined by a single layer of cells with clear cytoplasm (× 200); C: Low-grade nuclear features (Fuhrman nuclear grade 1) are seen and clear cells are present within the cyst wall and on the surface lining (× 400).

frequent in females[11]. MTSCC has a similar gross appearance to papillary RCC. Similarly, the immunohistochemical staining pattern of MTSCC is nearly identical to papillary RCC (positive for CK7 and AMCAR, and negative for CD10 and RCC-marker)[12], leading some to speculate that they may be a variant of papillary RCC[13]. However, genetic studies have shown that MTSCC does not show the characteristic molecular aberrations as seen in papillary RCC[14]. The characteristic gains of chromosome 7 and 17 and loss of chromosome Y typically seen in papillary RCC are not seen in MTSCC[14], which instead displays frequent losses and gains of other chromosomes[15].

MTSCC is a rare neoplasm, and can be a difficult diagnosis due to its morphologic heterogeneity. A study by Fine *et al*[16] describes the histologic variations of MTSCC and, in particular, what they described as the "mucin-poor variants". These variants show a predominance of tubular or spindle cell components and only minimal pale mucinous background. In addition, focal papillations or papillary cores and foamy histiocytes can be seen, creating confusion with papillary RCC. They note that helpful features in recognizing these variants are bland cytologic features and adjacent tubular and spindle cell components. It is important to be aware that focal areas of clear cells and oncocytic change can also be present[16].

MTSCC is considered a low-grade entity, with only rarely described cases of lymph node metastasis and recurrence. However, two cases of MTSCC with sarcomatoid change have been described, one with widespread metastasis to distant organs, including lung and bone[17]. A spindled component is characteristic of MTSCC, but the presence of significant pleomorphism with prominent nucleoli and mitotic activity, and necrosis should raise concern for a sarcomatoid change[17]. Microscopic necrosis alone can be seen focally in MTSCC, but it's significance is unknown. The presence of any necrosis should be mentioned in the final diagnosis[16].

Multilocular cystic clear cell RCC

Multilocular cystic clear cell RCC is defined as a distinct entity in the 2004 WHO classification. It is defined by the presence of low-grade clear cells lining cystic spaces and by the lack of a solid or expansive nodular component (Figure 3)[18]. Clear cells are commonly seen within the cyst wall (Figure 3), and can sometimes be difficult to distinguish from histiocytes. However, the neoplastic clear cells will be positive for cytokeratin and carbonic anhydrase IX (CA-IX), distinguishing them from histiocytes[19].

Multilocular cystic RCC shares similar genetic abnormalities with clear cell RCC, *i.e.*, the characteristic 3p deletions[20]. However, there have been no reported cases of progression or metastasis of this tumor, with a 5-year survival of 100%. In fact, the prognosis of this tumor is so favorable that, in the largest review utilizing the strict 2004 WHO criteria (45 cases), they suggested renaming this entity "multilocular cystic renal cell neoplasm of low malignant potential" and conservative management was suggested[21].

The distinction between a low grade (Fuhrman nuclear grade 1-2) clear cell RCC or clear cell papillary RCC can be difficult. A recent paper by Williamson *et al*[19] examined the immunohistochemical characteristics of multilocular cystic RCC. In contrast to conventional clear cell RCC, they found that CK7 was frequently diffusely positive and CD10 was less frequently positive in multilocular cystic RCC. This is similar to clear cell papillary RCC, which is also typically cystic. However, the absence of true papillae and the lack of CA-IX apical staining should distinguish these two entities[19]. Clear cell RCC with extensive cystic or necrotic change is important to include in the differential. Clear cell RCC will typically have large solid areas of neoplastic cells, which are not present in multilocular cystic RCC.

Carcinoma associated with neuroblastoma

Carcinoma associated with neuroblastoma is a distinct entity included in the 2004 WHO classification. It is defined as RCC which occurs in survivors of neuroblastoma[22]. A series of four cases from 1999 described RCC with papillary and solid patterns, abundant cytoplasm, and occasional oncocytic morphology, which occurred in patients with a previous diagnosis of neuroblastoma[23]. The tumors initially described were considered a distinct subset, morphologically and genetically distinct from other RCC subtypes. In recent years, Xp11 translocation

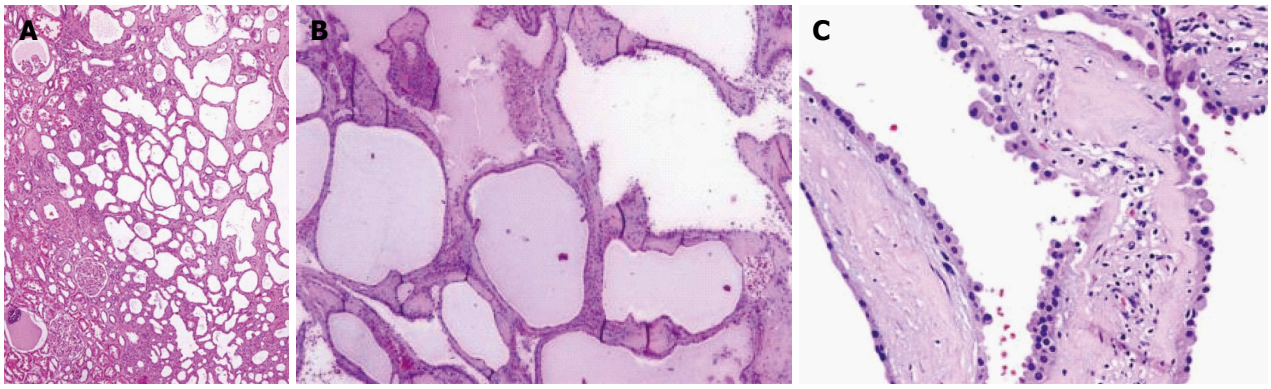

Figure 4 Tubulocystic carcinoma (hematoxylin and eosin). A: Tubulocystic carcinoma, on low power, is composed of many small cystic spaces with intervening fibrous septae (× 20); B: The cysts vary in size and shape (× 40); C: On higher power, bland cuboidal and hobnail-shaped cells are identified lining the cystic spaces (× 200).

RCC and papillary RCCs have also been described in neuroblastoma survivors[7,24,25].

The risk of developing another malignancy after neuroblastoma is well known[26]. RCC is the second most common type of such tumor, following thyroid carcinoma[26]. A survey of survivors of childhood cancer found a 329-fold risk of RCC in children with neuroblastoma[27]. The health risk after neuroblastoma is not limited to malignancy. A survey of 954 neuroblastoma survivors found an 8-fold likelihood of chronic health conditions, compared to their matched siblings, including musculoskeletal complications, endocrine abnormalities, and sensory abnormalities such as deafness and blindness. Many of these long-term effects are associated with treatment, which could also be associated with development of RCC[7]. However, there is evidence that the carcinoma associated with neuroblastoma is not related to therapy, but instead to an underlying genetic defect that predisposes individuals to development of cancer[23,27]. Regardless of the pathogenetic mechanism, knowledge of this entity in neuroblastoma survivors is essential for monitoring and early diagnosis.

RECENTLY DESCRIBED TUMORS

Tubulocystic carcinoma

Tubulocystic RCC is a recently described tumor composed of variably sized cystic tubules lined by a single epithelial layer with intervening fibrotic stroma (Figure 4). The neoplastic cells lining the cystic spaces have eosinophilic cytoplasm, hobnail nuclear morphology, and prominent nucleoli[28]. Tubulocystic RCC is not currently recognized by the WHO. However, accruing evidence suggests tubulocystic RCC merits consideration as a distinct entity.

Tubulocystic RCC was initially believed to derive from the collecting duct; in fact, it was originally considered a well-differentiated variant of collecting duct carcinoma. However, recent gene expression profiling evidence tends to refute this possibility[29]. The immunohistochemical staining pattern, ultrastructural features, and gene expression profiling favor a proximal convoluted tubule or intercalated cell origin[28,29]. In fact, some suggest that tubulocystic RCC may be closely related to papillary RCC[30,31]. One study of tubulocystic RCC found that 5 of their 13 cases of TCRCC had coexistent papillary renal cell neoplasms. In addition, a similar immunohistochemical staining pattern and gene expression profile between papillary RCC and TCRCC was identified[30]. This finding was supported by another study, which had 10 of 12 TCRCC cases with associated papillary neoplasms, including admixed TCRCC and papillary RCC in 4 cases[31]. This study also found gains of chromosome 17 in 8 of 12 cases of TCRCC[31]. Synchronous TCRCC with clear cell RCC has also been reported[32].

The largest clinicopathologic study to date on TCRCC was compiled by Amin *et al*[28] in 2009. They found TCRCC is more common in males and is a low-grade entity, with the majority of tumors presenting as stage pT1. Often, the tumor is an incidental finding. Tumors were both subcapsular (61.5%) and cortico-medullary or medullary (38.5%) in location. Only one case had local recurrence (3%) and two cases (6%) developed metastases. All cases had a Fuhrman nuclear grade of 3 despite an indolent behavior in the majority of cases, suggesting little value of Fuhrman grading in these neoplasms[28].

The differential diagnosis includes other cystic renal neoplasms, including multilocular cystic RCC. Focal cytoplasmic clearing has been noted in TCRCC[28]. Multilocular cystic clear cell RCC typically has lower Fuhrman grade nuclei, and scattered clear cells will be seen within the intervening fibrous stroma. Cystic nephroma could also be considered, but typically has larger cystic spaces and inconspicuous nucleoli. Mixed epithelial and stroma tumor also has cystic spaces, but will display an ovarian-type stroma. Oncocytoma with prominent tubules and cysts could also be considered, but typically will have nests of oncocytic cells, which are not present in TCRCC[28].

Thyroid-like follicular carcinoma of kidney

Thyroid-like follicular RCC was first described by Jung *et al*[33] in 2006. They described a case of primary renal carcinoma with morphology similar to a thyroid follicular carcinoma[33]. To date, only about 10 cases of this entity

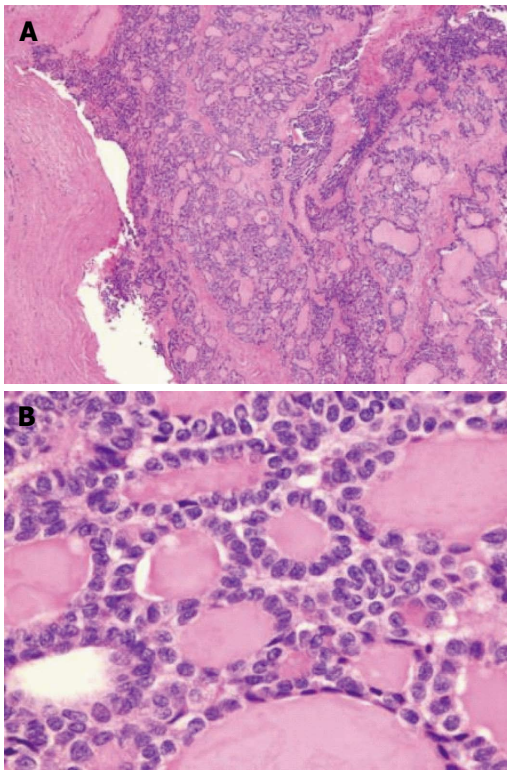

Figure 5 Thyroid-like follicular carcinoma of kidney (hematoxylin and eosin). A: The tumor has thyroid-like follicles filled with colloid-like material on low power (× 40); B: On high power, cells with enlarged, irregular nuclei and follicular architecture, similar to the follicular neoplasms of the thyroid, are seen; Nuclear grooves are also evident (× 400). Courtesy of Dr. Pheroze Tamboli, MD Anderson Cancer Center.

have been described in the literature[33-37].

The largest case series to date was compiled by Amin *et al*[34] in 2009 and includes 6 cases. They describe well-circumscribed tumors which grossly resemble thyroid parenchyma. The microscopic morphology mimics follicular carcinoma of the thyroid and contains colloid-like material (Figure 5). They are predominantly of low grade, but metastases to lymph nodes and to the lungs have been reported[34,35]. Six of the 10 reported cases in the literature occurred in patients in the 2nd and 3rd decades of life. However, the age range is wide, with cases reported from 29-83 years. Equal gender distribution is seen, and most of the cases are incidental findings (7 of 10 cases). No deaths from disease have been reported[37].

Distinction from a metastatic thyroid carcinoma is essential. The characteristic morphology and negative staining for thyroglobulin and thyroid transcription factor 1 confirms the diagnosis. The differential diagnosis also includes metastases from a teratoma (struma ovarii). Thyroidization of the kidney is also common in end-stage renal disease, but the cells lining the tubules are bland. Also, end-stage renal disease, in general, does not form a distinct tumor mass.

Acquired cystic kidney disease-associated RCC

Renal tubular cystic changes may develop in end-stage renal disease (ESRD), and this condition is termed acquired cystic kidney disease (ACKD). Renal tumors often occur in kidneys with ESRD with or, less frequently, without ACKD. The risk of RCC in patients with ACDK is greater than 100 times that of the general population, although the incidence is less than 10%[38-41]. A prior history of dialysis is often associated with the development of ACDK and RCC, with direct correlation to duration of dialysis[42]. The various tumor types encountered in cases with ESRD include the three common subtypes of RCC, *i.e.,* clear cell (conventional) RCC, papillary RCC, and chromophobe RCC, with papillary RCC as the most common. However, there are at least two other subtypes of RCC that are more frequently associated with ESRD: ACKD-associated RCC and clear cell papillary RCC. ACKD-associated RCC is reported only in patients with ESRD and ACKD, thus the name; whereas clear cell papillary RCC can be seen in patients with both cystic and non-cystic ESRD, as well as in those without ESRD[42-44].

The ACD-associated RCC is usually multifocal and bilateral. These tumors may be incidentally discovered on imaging studies or in nephrectomy specimens performed for renal cysts with complications or renal parenchymal bleeding, which not infrequently masks the underlying tumor. Most tumors are well circumscribed, and often appear to arise within cysts. Tumors which are larger in size are grossly solid with a thick, fibrous capsule and may be accompanied by foci of necrosis and hemorrhage.

Microscopically, the tumors demonstrate a growth pattern comprised of various proportions of acinar, alveolar, solid, cystic, and papillary architectural patterns. Tumor cells display characteristic features, including abundant granular, eosinophilic cytoplasm and large nuclei with prominent nucleoli (Figure 6). A cribriform or sieve-like appearance is characteristic and present in most cases. Most, but not all, cases also show intratumoral oxalate crystals, a relatively specific feature quite consistently observed in ACD-associated RCC and not in other tumor types[42,45]. Immunohistochemical stains aid in distinguishing these tumors as ACD-associated RCC stains diffusely positive for a-methylacyl-coenzyme A racemase (AMACR), but is negative or only focally positive for CK7. Stains for CD10, RCC antigen, and glutathione S-transferase A are also reported to be positive[46]. On a molecular level, these tumors do not show trisomy of chromosomes 7/17 or loss of 3p, characteristic of papillary and clear cell RCC, respectively. A recent study by Pan *et al*[46] on 9 cases of ACD-associated RCC showed variable combined gains of chromosomes 3, 7, 16, 17, and Y using fluorescence *in situ* hybridization and comparative genomic hybridization. It is also important to note that the nonneoplastic renal parenchyma often contains cysts lined by large eosinophilic cells that show an immunophenotype similar to that of ACD-associated RCC.

The biologic behavior of RCCs in ESRD in general is reported to be less aggressive than that of the RCCs in non-ESRD settings. These tumors often present at a lower stage and are smaller in size[47]. However, there are

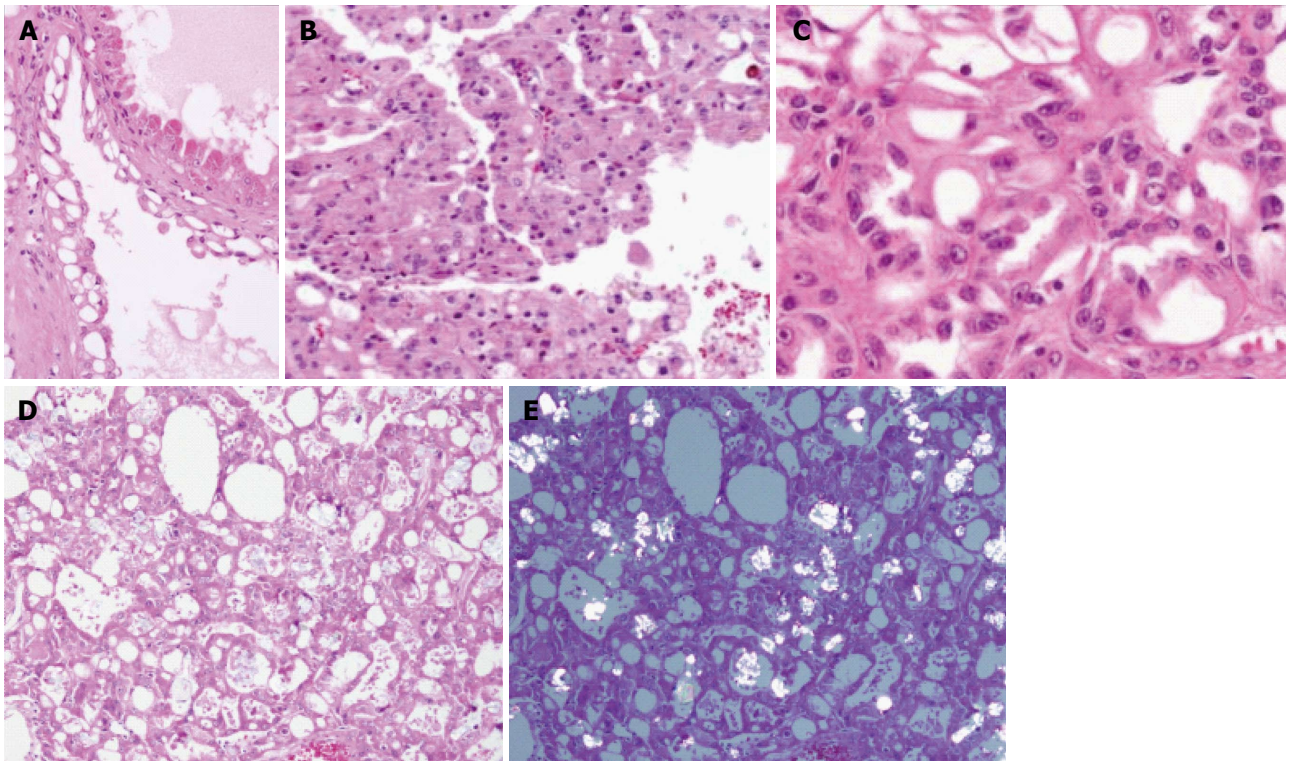

Figure 6 Acquired cystic disease-associated renal cell carcinoma. A, B: The tumor cells in acquired cystic disease-associated renal cell carcinoma typically have abundant eosinophilic cytoplasm and are seen lining the cystic spaces (A, × 400), and sometimes also show a solid growth pattern (B, × 200); The tumor characteristically arranges in a sieve-like cribriform pattern; C: The nuclear features are consistent with a Fuhrman nuclear grade 3, with prominent nucleoli (× 600); D, E: Calcium oxalate crystals are often associated with these tumors, and can be seen on hematoxylin and eosin staining (D, × 600) and with polarization (E, × 100).

a few case reports with metastasis or aggressive behavior. ACD-associated RCC may have a greater potential for aggressive behavior than other tumor types in ESRD. Rare cases with sarcomatoid features and unfavorable clinical outcomes have been reported[43,48].

The exact mechanisms underlying the increased incidence of RCC in ESRD, especially in those with superimposed ACDK are not completely understood. Multiple molecular alterations in diverse types of renal tumors indicate an acquired mechanism for renal tumorigenesis. Possible precursor lesions in ESRD include papillary adenomas and dilated tubules or clustered microcystic lesions lined by the eosinophilic cells[49]. Further research is necessary in order to delineate an etiologic relationship for these tumors.

Clear cell papillary renal cell carcinoma

Clear cell papillary RCC is a recently recognized renal tumor. This tumor was originally described in a background of ESRD and ACKD, although it has subsequently been reported in normal kidneys[42,43,50]. Metastasis from a clear cell papillary RCC has not been reported, highlighting the likelihood that these tumors are less aggressive than other RCC subtypes[42-44,50-53].

Clear cell papillary RCC is usually small and grossly encapsulated. The tumors may be solid, white tan, pale yellow or reddish brown in external appearance; however, the typical bright or golden-yellow heterogeneous cut surface of clear cell RCC is not identified. The cystic component is usually located at the periphery of the tumor, near its junction with renal parenchyma, and may be angulated, flattened, or irregular. Bilaterality and multifocality have been documented, especially in tumors arising in a background of ACKD[42-44,50-53].

On microscopic examination, clear cell papillary RCC is composed of a varying admixture of cystic, glandular, solid, and papillary components. The tumor cells have clear cytoplasm and are usually of low nuclear grade (Figure 7). One of the most distinctive features of clear cell papillary RCC is the linear positioning of the nuclei away from the basement membrane (inverted polarity). It is the presence of this feature within these tumors that aids in identification, irrespective of the architectural growth pattern, which can be markedly variable[43,44]. Papillary architecture is almost always present, but may be focal, and is commonly branched. Stellate tubular structures may also be seen. Some cases may have a prominent tubular pattern, as supported by previous reports describing this entity as tubulopapillary carcinoma. Other growth patterns include cystic, alveolar/nested, and retiform[43,50]. These tumors often have a fibrous capsule of varying thickness and often have variable amounts of eosinophilic hyalinized or sclerotic stroma[42-44,50-53]. Clear cell papillary RCCs sometimes contain foci of calcification or ossification, often within the tumor pseudocapsule[53].

In most cases, the morphologic features of clear cell papillary RCC are unique enough to allow for distinction from clear cell RCC based on HE-stained slides. In some

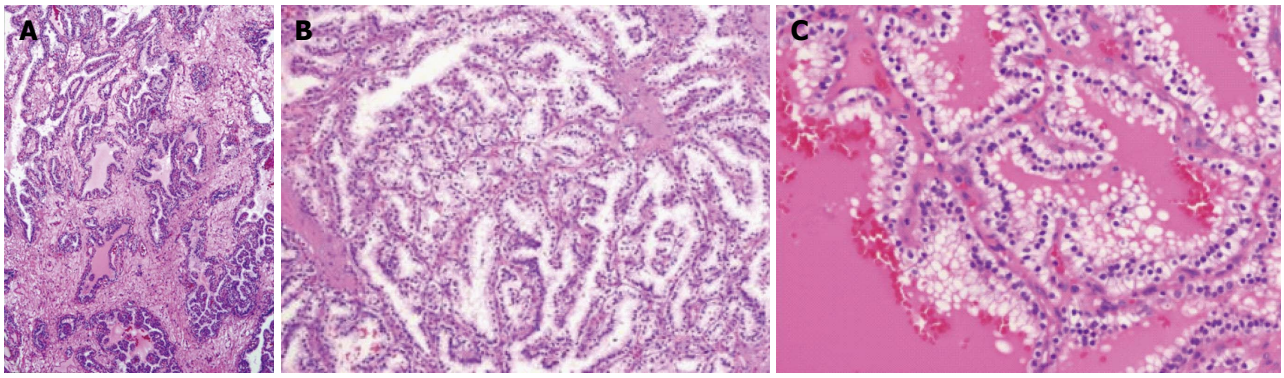

Figure 7 Clear cell papillary renal cell carcinoma (hematoxylin and eosin). A: The tumor has both a tubular and papillary architecture within a dense fibrous stroma (× 40); B: Other areas show a tubulopapillary growth pattern with delicate fibrovascular cores and conspicuous cytoplasmic clearing (× 100); C: The characteristic clear cells with low Fuhrman nuclear grade are seen with inverted linear positioning of the nuclei away from the basement membrane (× 200).

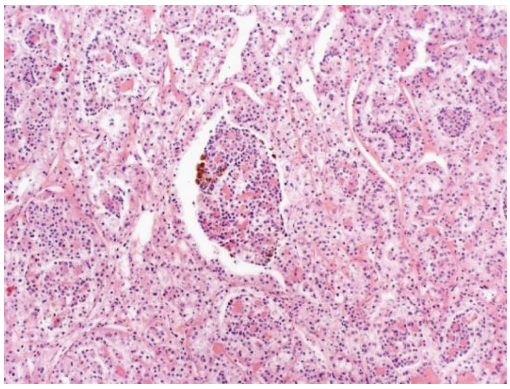

Figure 8 Renal cell carcinoma with t(6;11) translocation (hematoxylin and eosin). The tumor is composed of large epithelioid cells with abundant clear to eosinophilic cytoplasm; the distinctive feature of hyaline material with surrounding cells "rosette forming" is seen (× 100). Courtesy of Dr. Liang Cheng, Indiana University.

cases, immunohistochemical stains can be helpful, as clear cell papillary RCC and clear cell RCC have different immunoprofiles. Both clear cell papillary RCC and clear cell RCC typically express CA-IX, but the former usually exhibits weak expression, which is localized to the basal and lateral aspects of the tumor cells, so-called cup-shaped expression[44]. CD10 and 34βE12 show variable expression in these 2 tumor types, with the former more frequently positively expressed in clear cell papillary RCC. CK7 appears to be the most reliable marker for differentiating these 2 entities, as it is nearly always diffusely, strongly positive in clear cell papillary RCC, while only infrequently positive in clear cell RCC[43,44]. In general, when CK7 labeling is present in a clear cell RCC, it is focal or, at most, patchy and centered around cystic spaces[44]. Expression of AMACR is usually negative in both of these tumor types; thus, it is not of any use in this differential, but it can be extremely useful in cases of clear cell papillary RCC if the differential diagnosis includes papillary RCC[42-44,50-53].

Molecular changes in clear cell papillary RCC are distinctly different from those identified in clear cell and papillary RCCs. Sporadic clear cell papillary RCCs lack *VHL* mutations, 3p25 deletions, hypermethylation of the VHL promoter, and other recurrent copy number changes which are characteristically seen in clear cell RCCs. Of the cases reported to date, there has been only 1 *VHL* mutation occurring in a clear cell papillary RCC in a patient with known VHL disease, and 1 case of loss of heterozygosity of the *VHL* locus has been described[43]. Although low copy number gains of chromosomes 7 or 17 have been documented in a small subset of cases, the vast majority of clear cell papillary RCCs do not exhibit these findings[43,44,54,55]. No pathognomonic genetic alteration has been identified. However, a recent gene expression profile meta-analysis of clear cell RCC by Brannon *et al*[56] identified 3 distinct molecular subgroups within clear cell RCC. One of these groups corresponded to a VHL wild-type pattern of gene expression and, from the images provided in the article, morphologically appears to represent clear cell papillary RCC. This study highlights the fact that many clear cell papillary RCCs were incorrectly diagnosed as clear cell RCC in the past, while also emphasizing that clear cell papillary RCC and clear cell RCC are distinct entities.

CANDIDATE ENTITIES

RCC with t(6;11) translocation

An extremely rare subset of renal translocation tumors is associated with t(6;11) (p21;q12)/Alpha-TFEB gene fusion. This distinctive tumor was first described by Argani *et al*[57] in 2001. Since then, a handful of cases of this rare entity have been documented in the literature. TFEB RCCs are predominantly seen in younger patients and are generally indolent, with rare reported cases of metastatic disease[58-66]. The most common histologic pattern is large epithelioid cells with voluminous clear to slightly eosinophilic cytoplasm, and clusters of small cells, usually clustered around hyaline material (rosette-forming) (Figure 8). However, TFEB RCCs may demonstrate unusual morphologic features, such as papillary, tubular, chromophobe RCC, clear cell RCC, and epithelioid angiomyolipoma-like structures[58-66].

A recently developed antibody to TFEB and cathep-

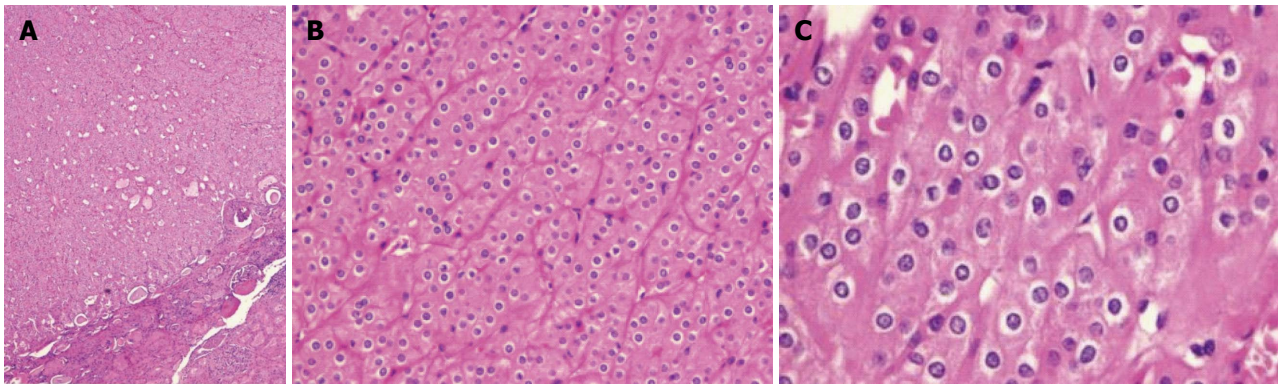

Figure 9 Hybrid oncocytoma/chromophobe renal cell carcinoma (hematoxylin and eosin). A: Low power assessment of the tumors shows a well-circumscribed tumor with a solid growth pattern (× 40); B: The tumor cells have abundant eosinophilic cytoplasm and round, monotonous nuclei (× 200); C: Perinuclear halos are prominent throughout, with some areas showing mild nuclear irregularity (× 400). The overlapping features of oncocytoma (round nuclei with abundant eosinophilic cytoplasm) and chromophobe (perinuclear halos) are noted.

sin K proteins is highly sensitive and specific for TFEB RCCs[58,67]. It is important to recognize there must be nuclear positivity for TFEB, as the fusion product will be present in the nucleus. Non-translocated TFEB can cause falsely positive cytoplasmic staining[58]. Both *TFEB* and *TFE3* (described above in Xp11 translocation RCC) are part of the microphthalmia transcription factor/transcription factor family translocation RCCs. Overexpression of *TFE3* and *TFEB* in these neoplasms is known to increase the expression of cathepsin K proteins[67]. A study by Martignoni *et al*[67] showed that 7 of 7 TFEB RCC and 6 of 10 Xp11 translocation RCC had strong expression of cathepsin K, which was not seen in any other renal neoplasms[67]. In the study by Rao *et al*[66], all of the tumors showed moderate to strong immunoreactivity for TFEB, Ksp-cadherin, and vimentin, but were negative for TFE3, CD10, and CK7. Cathepsin K, HMB45, and melan A are moderately or strongly expressed in TFEB RCCs[58-67].

TFEB RCCs are often diagnosed based upon their distinctive morphology and immunophenotype. However, molecular methods such as PCR, RT-PCR, and FISH are extremely helpful and sometimes mandated for an accurate diagnosis. An interphase FISH assay is useful in the definitive identification of TFEB RCCs, and plays an essential role in identifying previously undiagnosed cases[66,68].

As these are rare tumors, there is still a degree of uncertainty regarding the final clinical outcome of patients. In the study by Rao *et al*[66], all 6 patients with follow-up available were alive with no recurrent disease. Their follow-up ranged from 6 to 55 mo, with a mean follow-up time of 31 mo. Other studies have shown a similar good prognosis[59,61], and TFEB RCC appears to be a relatively indolent tumor. However, further studies are warranted to determine long-term clinical outcomes.

To detect this tumor, we recommend the same approach of immunostains as for Xp11 translocation carcinoma in young patients under 30. If the initial cytokeratin stain is negative or weakly to focally positive, a TFE3 stain is recommended. If the TFE3 stain is negative, TFEB and HMB45 immunostains are recommended to diagnose a RCC with t(6;11) translocation tumor (both TFEB and HMB45 positive), and exclude the possibility of epithelioid angiomyolipoma (TFEB negative and HMB45 positive).

Hybrid oncocytoma/chromophobe RCC

Hybrid oncocytoma/chromophobe RCC was first recognized in patients with Birt-Hogg-Dubé (BHD) syndrome, a rare autosomal dominant condition characterized by fibrofolliculomas, renal tumors, pulmonary cysts, and spontaneous pneumothorax[69]. Mutation of the *BHD* gene on chromosome 17, a tumor suppressor gene, is attributed to this syndrome[70]. The renal tumors in these patients are characterized by the morphologic features of both oncocytoma and chromophobe RCC within the same tumor, known as hybrid oncocytoma/chromophobe RCC[69]. BHD patients also have an increased incidence of other RCCs, including chromophobe and clear cell RCC. The renal tumors in BHD patients are frequently bilateral and multifocal, and background renal oncocytosis within the kidney may be seen[69]. Renal oncocytosis is characterized by oncocytic change in the renal tubules and multiple oncocytomas.

Hybrid oncocytoma/chromophobe has been described as occurring in patients with renal oncocytosis; however, there has been an increased recognition of this entity in sporadic tumors without a background of renal oncocytosis or BHD syndrome[71-73]. These tumors are composed of cells with abundant granular eosinophilic cytoplasm, round nuclei, perinuclear halos, and CK7 positivity (Figure 9). Some of these sporadic hybrid tumors have distinctly different morphology in separate areas, while others have mixed features throughout[71].

The heightened awareness of hybrid tumors leads to questions of the utility of core needle biopsy in oncocytic neoplasms, which may miss a chromophobe component in a hybrid tumor due to sampling error. The distinction between oncocytoma and chromophobe RCC is clinically important, and the behavior of these hybrid entities is yet unknown. However, small, retrospective studies have

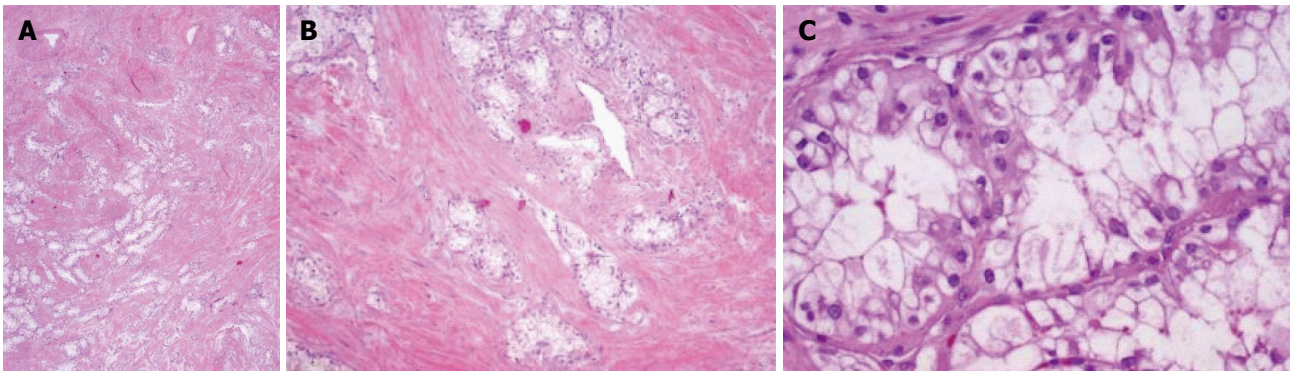

Figure 10 Renal angiomyoadenomatous tumor (hematoxylin and eosin). A, B: The tumor is composed of epithelioid cells in a background of dense, leiomyomatous stroma (A, × 40 and B, × 100); C: The tumor cells have oval nuclei of low Fuhrman nuclear grade with clear to eosinophilic cytoplasm and protrude into the lumen, resembling a so-called "shark's smile" (× 400). Courtesy of Dr. Melissa Stanton, Mayo Clinic, Arizona.

shown that these hybrid oncocytoma/chromophobe tumors have a clinically indolent course[73]. Further studies are needed to determine the behavior and pathogenesis of these neoplasms.

Hereditary leiomyomatosis and RCC syndrome

Hereditary leiomyomatosis and RCC (HLRCC) is an autosomal dominant familial syndrome characterized by the development of cutaneous and uterine leiomyomata, as well as renal tumors[74]. The hallmark mutation in this syndrome is the fumarate hydratase (*FH*, 1q42.3-q43) gene, but the exact prevalence of HLRCC is unknown. Kidney cancers are less penetrant than the leiomyomatous manifestations in HLRCC-affected families[75-77]. The association between cutaneous and uterine leiomyomata has been known for many years as Reed syndrome[78].

The renal tumors in this syndrome are aggressive, as demonstrated by the fact that 9 out of 13 patients in the first reported cohort of North American families died of metastatic disease within 5 years of initial diagnosis[75]. Other studies have shown lymph node metastasis is common, and there is a poor prognosis[79]. In the largest series published by Merino *et al*[79], 40 renal tumors resected from 38 HLRCC patients with proven fumarate hydratase germline mutations were studied. The patient age ranged from 17 to 75 years and tumors ranged in size from 2.3 to 20 cm. A papillary architecture was most common (25 of 40 cases), but tubulopapillary, tubular, solid, and mixed patterns were also seen. Immunohistochemical stains were nonspecific. The defining characteristic of HLRCC, as described by Merino *et al*[79], is the presence of a large nucleus with a prominent inclusion-like eosinophilic nucleolus, surrounded by a perinucleolar clearing. This distinctive morphology is also seen in the leiomyomata of these patients (described below).

Leiomyomatosis is a condition defined by the occurrence of multiple leiomyomas throughout the body, with often poorly defined nodules involving areas of the skin on the arms, chest, legs, and, in extremely rare cases, the uterus. In a study by Sanz-Ortega *et al*[80], uterine leiomyomata were identified in HLRCC patients at a young age (median age of 32 years). They were often multiple and ranged from 1 to 8.5 cm in size. Histopathologically, HLRCC leiomyomata frequently had increased cellularity, multinucleated cells, and atypia. All cases showed tumor nuclei with large orangeophilic nucleoli surrounded by a perinucleolar halo similar to the changes found in HLRCC[79]. This study also showed that loss of heterozygosity (LOH) at 1q43 was frequent in HLRCC leiomyomas (8/10 cases), similar to the molecular alterations in renal tumors. LOH is considered to be the second hit that inactivates the *FH* gene, and FH mutations and LOH at 1q43 are unusual in sporadic leiomyomas.

Uterine leiomyomas and renal tumors in HLRCC share similar morphologic changes and genotypic features. It is important to recognize these features in leiomyomata so patients undergo early genetic testing for germline *FH* mutations and screening for renal cell cancer.

Renal angiomyoadenomatous tumor

Michal *et al*[81] reported a series of 5 cases which they designated as renal angiomyoadenomatous tumor, wherein the tumors were composed of clear cells, leiomyomatous stroma, and adenomatous structures with apical snouting (described as resembling a "shark's smile") (Figure 10). The epithelial tumor cells were positive for EMA, CK7, CK20, AE1-AE3, CAM5.2, and vimentin. In this series of cases, no *VHL* mutation was identified.

Cases of clear cell papillary RCC with smooth muscle metaplasia of intratumoral stroma, also recently described as "RCC with angioleiomyoma-like proliferation" or "clear cell RCC with smooth muscle stroma", share a significant degree of morphologic overlap with this entity[82,83]. It is currently debated whether these two tumors are related, or perhaps even variants of the same tumor[84-88]. Losses of chromosome 3 and 3p have been demonstrated in at least a subset of these tumors[83]. Some studies report that these lesions have demonstrated abnormalities of chromosomes 3 and the *VHL* gene, in addition to abnormalities of chromosomes 1, 11, and 16[83,85,86,88].

CONCLUSION

Our understanding of RCC continues to evolve. The

review of recent updates in selected tumors herein will hopefully serve as a useful prognostic and treatment guide for both the urologist and surgical pathologist, particularly in the era of personalized medicine.

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MINIREVIEWS

Etiology of non-traumatic acute abdomen in pediatric emergency departments

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Abstract

Acute abdominal pain is a common complaint in pediatric emergency departments. A complete evaluation is the key factor approaching the disease and should include the patient's age, any trauma history, the onset and chronicity of the pain, the related symptoms and a detailed physical examination. The aim of this review article is to provide some information for physicians in pediatric emergency departments, with the age factors and several causes of non-traumatic acute abdominal pain. The leading causes of acute abdominal pain are divided into four age groups: infants younger than 2 years old, children 2 to 5, children 5 to 12, and children older than 12 years old. We review the information about acute appendicitis, intussusception, Henoch-Schönlein purpura, infection, Meckel's diverticulum and mesenteric adenitis. In conclusion, the etiologies of acute abdomen in children admitted to the emergency department vary depending on age. A complete history and detailed physical examination, as well as abdominal imaging examinations, could provide useful information for physicians in the emergency department to narrow the differential diagnosis of abdominal emergencies and give a timely treatment.

Key words: Abdominal pain; Non-traumatic acute abdominal pain

Core tip: The mini review provides the essential information for physicians in pediatric emergency departments, mainly focused on the clinical diagnosis in different age groups and on several major causes of acute abdominal pain in children.

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INTRODUCTION

A common complaint in pediatric emergency departments (ED), abdominal pain is sometimes hard to assess in ill children due to the variation of pain degree, the difficulty in describing it, and being localized to the abdomen. Although most children with abdominal pain have a self-limiting course, some critical medical and surgical emergencies may occur in the ED. The diverse etiologies include acute surgical disease, intra-abdominal medical disorders, extra-abdominal conditions, systemic illness and, commonly, functional abdominal pain. A timely diagnosis is necessary for preventing further complications

Table 1 Differential diagnosis of acute abdominal pain by predominant age

Younger than 2 yr	2 to 5 yr	5 to 12 yr	Older than 12 yr
Infantile colic	Gastroenteritis	Gastroenteritis	Appendicitis
Gastroenteritis	Appendicitis	Appendicitis	Gastroenteritis
Constipation	Constipation	Constipation	Constipation
UTI	UTI	Functional pain	Dysmenorrhea
Intussusception	Intussusception	UTI	Mittelschmerz
Volvulus	Volvulus	Trauma	PID
Incarcerated hernia	Trauma	Pharyngitis	Threatened abortion
Hirschsprung's disease	Pharyngitis	Pneumonia	Ectopic pregnancy
	Sickle cell crisis	Sickle cell crisis	Ovarian/Testicular torsion
	HSP	HSP	
	Mesenteric adenitis	Mesenteric adenitis	

UTI: Urinary tract infection; PID: Pelvic inflammatory disease; HSP: Henoch-Schonlein purpura.

and, of course, the possible legal problems. This article reviews the non-traumatic causes of acute abdominal pain in pediatric EDs.

Theoretically, abdominal pain results from visceral, somatic and referred pain. Visceral pain results from the distension of a viscus stimulating nerves and generally presents with a dull, poorly localized pain over the epigastric, periumbilical or suprapubic midline area. The somatic pain comes from the stimulation on somatic nerves in the parietal peritoneum, muscle or skin unilateral to the spinal cord level from T6 to L1, presenting as well localized, intense and sharp. Referred pain is felt distant from the diseased organs, characterized by either a sharp, localized sensation or a vague ache. However, all the pains above can present clinically with agonizing pains, making it hard for the pediatrician to take a history and accurate physical examination.

EVALUATION

The evaluation should begin with a competent clinical evaluation, including the patient's age, any trauma history, the onset and chronicity of the pain, the related symptoms and a detailed physical examination. Abdominal imaging is not always required but is sometimes invaluable for narrowing the differential diagnosis or confirming a diagnosis. When assessing the child who develops abdominal pain without a history of trauma in the pediatric ED, the first priority is stabilization if the child is seriously ill. It should be emphasized that abdominal emergency may progress to a shock status and cardiorespiratory shock can present with acute abdominal pain. The second priority is to identify the child who requires immediate or potential surgical intervention, such as acute appendicitis or bowel perforation. The third priority is to diagnose any medical illness from among a large group of acute and chronic abdominal and extra-abdominal inflammatory disorders that require emergency nonoperative management.

During diagnosis, the factors of age, chronicity and any presence of obstruction, peritonitis or a mass should be carefully considered.

AGE

Age is a very important factor when assessing abdominal pain in children and the prevalence of each etiology varies greatly in children of different age groups (Table 1).

Infants younger than 2 years old

The infant with acute abdominal pain in this age group is very difficult for primary clinicians to evaluate because the only symptom may be inconsolable crying and finally lethargy. Bilious emesis is key information and must be taken seriously as a possibility of malrotation with volvulus. A contrast study of the upper gastrointestinal tract is necessary if no other cause is evident. The history taken should include the bowel movement pattern, presence of fever or diarrhea or even currant jelly stool, amount of vomiting and the timing, the sequence of pain and vomiting, and the presence of a productive cough.

Paralytic ileus, manifesting clinically with distension and absent bowel sounds, often accompanies surgical conditions, sepsis and infectious enterocolitis and should be closely followed up. An incarcerated hernia and intussusception are the two most common causes of bowel obstruction in this age range. Abdominal imaging could provide useful evidence of obstruction or perforation signs and any signs of partial or complete obstruction with peritonitis may indicate a perforated viscus from intussusceptions, volvulus or occasionally appendicitis or Hirschsprung's disease.

Infants with recurrent or chronic abdominal pain in this age group may not have any symptoms. The differential diagnosis includes recurrent intussusceptions, malrotation with intermittent volvulus, milk allergy syndrome and various malabsorptive diseases, such as lactase deficiency. Abdominal sonography should be arranged for any irritably crying infants or infants with lethargy for any evidence of intussusception. Reduction with air or barium is also indicated in cases of suspected intussusceptions which cannot be clearly and directly revealed by ultrasound. Abdominal computed tomography (CT) with contrast is indicated during the process of evaluation when clinicians are suspicious of serious

morbidity, such as complex abdominal masses and fluid accumulation.

Children 2 to 5 years old

Common causes of acute abdominal pain in this age group include inflammatory processes such as gastroenteritis and urinary tract infection (UTI). Preschool children may be able to verbally describe the types of abdominal pain and localize the site of pain. Related histories should be taken seriously. Some associated symptoms are helpful in the differential diagnosis, such as that lower gastrointestinal (LGI) bleeding may indicate infectious enterocolitis, intussusceptions, Meckel's diverticulum or inflammatory bowel disease *etc*. and extra-abdominal symptoms such as productive cough and pyrexia may be attributed to lobar pneumonia. A diabetic child with acute abdominal pain may be considered as having diabetes ketoacidosis. The important surgical causes of children with abdominal pain in this age group include acute appendicitis, intussusception and malrotation. Clinically ill children with abdominal pain may suffer from life-threatening diseases or some uncommon etiologies. Physical examinations of such patients may appear as jaundice (hepatitis, hemolytic anemia), rash or arthritis (anaphylactoid purpura), or cardiac murmurs (myocarditis). Moreover, chronic constipation starts to increase in frequency in this age group.

Right lower quadrant (RLQ) tenderness, especially persistent pain over here, should be always considered for the probability of acute appendicitis. The most specific finding of an abdominal plain film is the presence of a calcified appendicolith; however, this is only present in a minority of patients (< 10%)[1,2]. Besides, localized bowel obstruction and obliteration of the psoas shadow may be found in cases of acute appendicitis. Abdominal sonography should also be performed over the entire abdomen, including the pelvis area, to exclude any probability of ovarian torsion which is rarely noted but actually presents in female patients of this age group.

Children 5 to 12 years old

In this age group, nonorganic or psychogenic illness, or functional abdominal pain start to increase as causes of acute abdominal pain. The leading organic causes are still inflammatory processes, including gastroenteritis, appendicitis and UTI. If intussusception presents in this age group, a leading point, such as mesenteric adenitis, lymphoma, polyp and anaphylactoid purpura, should be sought for and abdominal ultrasound and CT may be helpful for clinicians to identify the leading points.

The description of abdominal pain is generally reliable in children in this age range. In clinical presentations, the presence of fever may come from infectious causes; diarrhea may be caused by infectious colitis, IBD from an appendiceal abscess irritating the bowel, urinary frequency and dysuria may increase the possibility of UTI. The clinical history of abdominal pain, beginning from the periumbilical area first and migrating to the RLQ of the abdomen after several to 24 h, may commonly present in older children suspected of having acute appendicitis.

Clinical presentations of functional abdominal disorders are generally episodic periumbilical, rarely occur during sleep, have no particular associations with eating and activity and are not of organic causes. Although a worrisome patient and parents may search for definite causes of recurrent abdominal pain, abdominal CT rarely helps. However, the premise is that the diagnosis of functional abdominal pain should be made through complete history, physical examination and even whole abdominal and pelvis ultrasound scan. Of course, if the abdominal pain still presents without improving after a period of light diet or no oral intake, further survey should be carried out, *e.g*. abdominal CT.

Children older than 12 years old

The history and physical examination of acute abdominal pain should be taken carefully, especially for female patients. Complete history taking should involve menstrual history and sexual activity, although it is often hard to ascertain.

Acute pain with peritonitis in adolescents usually results from acute appendicitis. In addition, the differential diagnosis should include testicular or ovary torsion and for females PID and ectopic pregnancy should be considered. Acute abdominal pain without peritoneal signs in males often results from gastroenteritis or a viral syndrome, whereas in females it may often be attributed to UTI or pyelonephritis.

In the ED, postmenarchal girls with abdominal pain should have a pregnancy test when pregnancy cannot be excluded. Ultrasound is often helpful to check the gestational sac and evaluate the condition of adnexa. Especially for the female patient with RLQ pain, sonography with color Doppler is helpful for differentiating acute ovarian torsion from appendicitis and may also be helpful for assessing ovary viability. Besides, some experts have suggested that ovarian cysts greater than 5 centimeters rarely cause ovarian torsion and most cases of ovarian torsion are secondary to adnexal pathology, such as ovarian tumors or cysts, and torsion of normal adnexa is less common.

ETIOLOGIES

The diverse etiologies include acute surgical disease, intra-abdominal medical ailments, extra-abdominal conditions, systemic illness and, commonly, functional abdominal pain. We review five non-traumatic causes of acute abdominal pain in the pediatric ED, including acute appendicitis, intussusception, Henoch-Schönlein purpura (HSP), infection, Meckel's diverticulum and mesenteric adenitis.

Acute appendicitis

Acute appendicitis is the most common condition re-

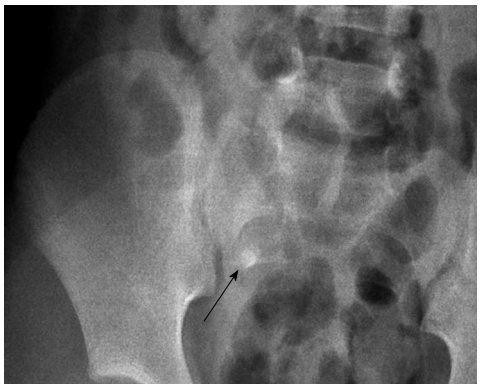

Figure 1 A nodular calcified appendicolith (arrow) in the right lower abdominal quadrant.

quiring emergency abdominal surgery in children and is ultimately diagnosed in 1% to 8% of children presenting to the pediatric ED with acute abdominal pain[2,3]. Clinically, the diagnosis of acute appendicitis is often based on a brief history, physical examination and laboratory findings. Common clinical appearances of acute appendicitis in children include migration of abdominal pain, RLQ tenderness, rebound pain, muscle guarding and vomiting. Very young children may reveal diarrhea as a presenting symptom. The classic constellation of symptoms in acute appendicitis is periumbilical pain followed by nausea, right lower quadrant pain, vomiting and fever. Unfortunately, this sequence is present in only less than one-third of all pediatric patients and is less common in children younger than 5 years of age[4]. Appendicitis may be missed at initial clinical examination in 28% to 57% of children aged 12 years or younger and in nearly 100% of children under 2 years old. Because of the difficulty in evaluating young children with abdominal pain, perforation rates for appendicitis are higher than in the general adult population (30% to 65%)[3,5].

No laboratory test is both 100% sensitive and 100% specific for diagnosing appendicitis. White blood cell count may be helpful in the diagnosis of appendicitis and the presence of elevated serum C-reactive protein (CRP) also has been studied as a biomarker for appendicitis. Moreover, the changes after short-term observation in percentage neutrophil counts on the first day of the onset of patients' symptoms (day 1) and CRP on day 2 and day 3 are relatively specific for diagnosing acute appendicitis and may be used to exclude other inflammatory conditions in the abdomen[6].

Plain film abdominal series are often obtained in children suspected of having acute appendicitis and the most specific finding is calcified appendicolith. Appendicoliths are present only in approximately 10% of true cases with appendicitis (Figure 1)[1,2,4].

Diagnostic imaging, including graded-compression US and helical CT, play an increasing role in the prompt and accurate diagnosis of acute appendicitis in children. The principal advantages of graded-compression US are its lower cost, lack of ionizing radiation and ability to

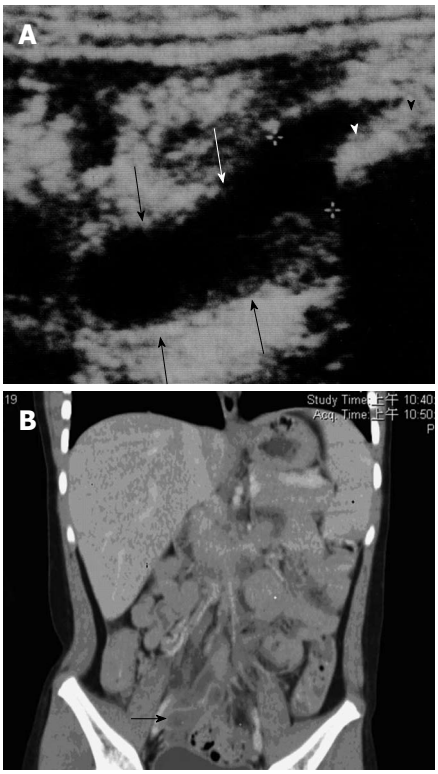

Figure 2 Acute appendicitis. A: A blind-ending, non-compressible tubular structure (arrows); an echogenic appendicolith with an acoustic shadow over tip (arrowheads); B: An enlargement of whole diameter of the appendix (arrows) with enhancement and thickening of the appendiceal wall associated with intraluminal fluid collections.

delineate gynecological disease. However, an important limitation of graded-compression US for the diagnosis of acute appendicitis is that the diagnostic accuracy is highly dependent on the skill of operators, as evidenced by the great variability in its reported diagnostic sensitivity and specificity for this condition. The reported sensitivity of US in children has ranged from 44% to 94% and the specificity has ranged from 47% to 95%[3]. An inflamed appendix is usually aperistaltic, difficult to compress and measures ⩾ 6 mm in diameter (Figure 2A). It is important for US performers to visualize the entire appendix to avoid a false-negative reading because sometimes only the distal tip of the appendix is inflamed. A periappendiceal fluid accumulation may indicate an early perforation but may simply result from inflammation.

CT has become the test of choice for surgeons when ultrasonography fails to give a definitive diagnosis. The reported sensitivity of CT for the diagnosis of acute appendicitis in children has ranged from 87% to 100% and the specificity has ranged from 89% to 98%[4,5]. Direct signs of CT for acute appendicitis include an enlarged appendix (> 7-mm transverse diameter), a nonopacified appendiceal lumen and significant wall enhancement with intravenous contrast material administration (Figure 2B). Secondary signs of acute appendicitis include periappendiceal fat stranding or free fluid in the RLQ of the abdomen or pelvis. Focal cecal wall thickening adjacent to an inflamed appendix has been given specific names:

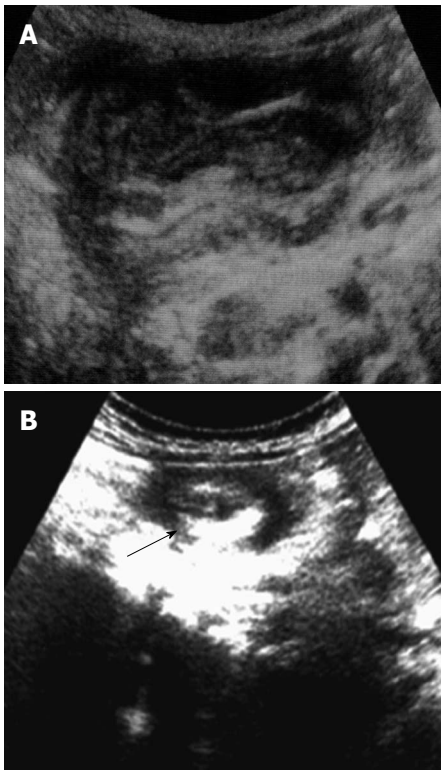

Figure 3 "Pseudokidney" sign (A) and "target sign (arrow)" (B) on ultrasonography.

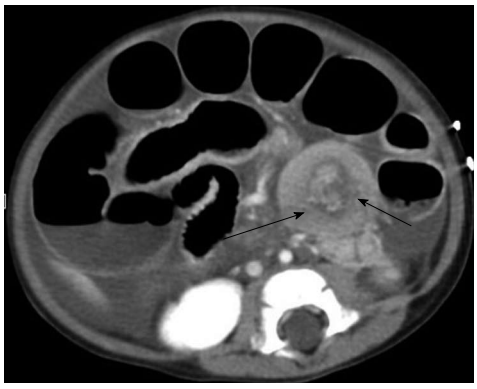

Figure 4 A concentric ring of the ileum (arrows) from ileo-colic intussusception.

focal cecal apical thickening, the so-called arrowhead sign which involves focal thickening of the cecum pointing toward an inflamed appendix, or the so called cecal bar in which an appendicolith is separated from a contrast material-filled cecum by an inflammatory process at the base of the appendix.

CT has dramatically improved our ability to detect appendicitis and its complications. It has led to improved patient outcomes and lessened the number of unnecessary surgeries. Magnetic resonance imaging (MRI) is also superior in its ability to diagnose appendicitis in children but it may not be available or practical.

When the diagnosis of appendicitis is made, preparing the child for the operating room is essential. If there are clinical or radiological signs of perforation, antibiotics with gram negative and anaerobic coverage should be started in the ED.

Intussusception

Intussusception, defined as an invagination of the proximal portion of the bowel into an adjacent distal bowel segment, is the second most common cause of intestinal obstruction in infants. It appears predominantly in males and the most common type is ileocolic invagination. Intussusception is seen most frequently between the ages of 3 mo and 5 years, with 60% of cases occurring in the first year and a peak incidence at 6 to 11 mo of age. In children younger than 2 years of age, a pathological lead point is found in less than 5% to 10% of cases[7,8]. However, pathological lead points are more common in older children, with Meckel's diverticulum being the most common. Other causes of lead points are submucosal hemorrhage from Henoch-Scholein purpura, lymphomas and intestinal polyp. The classic triad of intussusception, including intermittent colicky abdominal pain, vomiting and bloody mucus stools (currant jelly stools) is encountered in only 20% to 40% of cases[7]. At least two of these findings present in approximately 60% of patients.

A palpable sausage-like abdominal mass in the right upper or lower quadrant may be found but it is difficult to perform in crying infants.

Plain abdominal radiographs are usually the initial studies in children with possible intussusception. Moreover, they are neither sensitive nor specific for intussusception. Plain films may show a variety of abnormalities, including a visible abdominal mass, abnormal distribution of gas and fecal contents, air fluid levels and dilated loops of the small intestine. A "target sign" on plain film consists of concentric circles of fat density similar in appearance to a doughnut visualized to the right of the spine. Ultrasonography is useful for diagnosing intussusception and the classic findings, including the "target sign", a single hypoechoic ring with a hyperechoic center and the "pseudokidney" sign, superimposed hypo and hyperechoic areas representing the edematous walls of the intussusceptum and layers of compressed mucosa (Figure 3)[7].

CT may be considered in highly suspected bowel obstruction or surgical emergencies when US cannot determine a definite cause in children. However, CT would not be performed routinely in patients with suspected intussusception. The findings of intussusception on CT reveal bowel loops containing alternating high and low rings of attenuation and a dilated proximal small bowel with air-fluid levels (Figure 4).

Barium enema is the gold standard study for the diagnosis of intussusception and is also a therapy. However, air-contrast enema has been used for many years in some countries and has been shown to be as effective as barium enema for intussusception. Air contrast decreases the risks of chemical peritonitis caused by

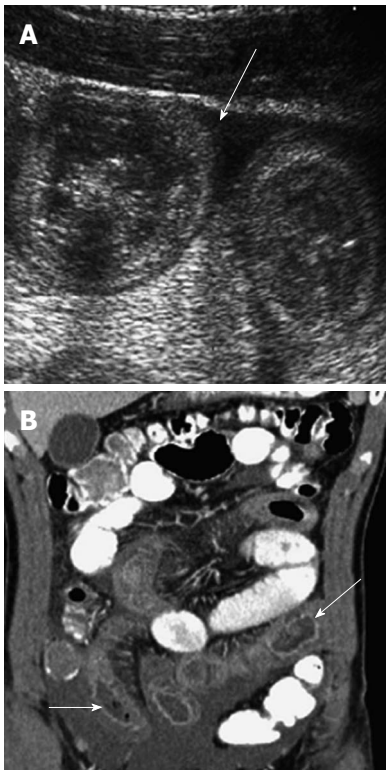

Figure 5 Henoch-Schonlein purpura. A: Sagittal ultrasound image shows more moderate wall thickening of small bowel with ascites; B: Coronal computed tomography shows long segments of thickened, enhancing, fluid filled small bowel (arrows).

perforation with barium enema in this disease. An ileo-ileac type of intussusception can be much harder to diagnose and is much harder to be released by air or barium reduction. Not every child with intussusception should undergo bowel reduction by enema. Clinical signs of peritonitis, bowel perforation and hypovolemic shock are clear contraindications to enemas. Relative contraindications to enemas include prolonged symptoms (≥ 24 h), evidence of obstruction, such as air fluid levels on plain abdominal films, and ultrasonography findings of intestinal ischemia or trapped fluid. Even in well-selected patients, enemas may cause the reduction of necrotic bowel, perforation and sepsis. After a successful reduction, the child should be admitted for observation. A small percentage of patients (0.5% to 15%) may have a recurrence of intussusception, usually within 24 h but sometimes after days or weeks. Even after reduction by laparotomy, the recurrence rate is approximately 2% to 5%[8,9].

HSP

HSP is the most common vasculitis of childhood and is an acute, systemic, self-limited, small-vessel vasculitis usually seen in otherwise healthy children. The incidence of HSP is reported as ranging from 6 to 22 cases per 100000 children in different populations. Although it most often affects young children, it may develop at any age. Most HSP occurs between 3 and 5 years of age and ninety percent of HSP patients are under 10 years of age. It is thought to occur more often in female children, although some have found a male predominance or both genders to be equally affected[5]. The etiology of HSP remains unknown, although many antigens, such as infective agents, vaccinations, drugs and insect bites are suspected. In 1990, the American College of Rheumatology published diagnostic criteria for HSP, including: (1) palpable purpura, that is slightly raised hemorrhagic skin lesions not related to thrombocytopenia; (2) age, 20 years or younger at onset of first symptoms of the disease; (3) bowel angina, that is diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea; and (4) wall granulocytes on biopsy, that is histological changes showing granulocytes in the walls of arterioles or venules. A patient is diagnosed with HSP if at least two of the four criteria are present; this yields a sensitivity of 87.1% and a specificity of 87.7%[10].

The disease usually lasts for 1 to 4 wk. The predominant cutaneous finding of HSP is painless, palpable purpura. In more than 70% of patients, palpable purpura alone or purpura associated with abdominal and/or joint pain is the first sign. Abdominal pain is the most common gastrointestinal symptom, affecting two-thirds of children. The pain is usually localized to the periumbilical or epigastric region and described as blunt in nature. Bowel wall thickening caused by vasculitis-associated ischemia has a mean thickness of 9 mm and involves longer segments than bowel thickening associated with hematoma (Figure 5)[11].

Treatment for children with HSP is mostly supportive, relieving associated arthralgia and abdominal pain. In patients with normal renal function, therapy should focus on the maintenance of hydration, nutrition and electrolyte balance. Most agree that analgesics and/or nonsteroidal anti-inflammatory agents should be used for the control of arthralgia and inflammation in children. Gastrointestinal involvement has been reported to occur in approximately 50% to 75% of patients with HSP[10,11]. Severe abdominal pain that is unresponsive to conventional treatments may respond dramatically to a trial of intravenous corticosteroids. Systemic steroids, such as oral prednisolone or pulsed intravenous methylprednisolone, may be effective in children with massive gastrointestinal hemorrhage and ischemic bowel.

Infections

AGE is the most common gastrointestinal inflammatory process in children. The cause is usually viral and rotavirus is the most common in children. Vomiting usually precedes the diarrhea by as much as 12 to 24 h. A low grade fever may or may not be associated with AGE. Examination of the abdomen usually reveals a nondistended soft abdomen with no localized tenderness (may be diffusely, mildly tender) and usually there is minimal to no guarding. AGE may cause an ileus in severe cases[12]. Viral diarrhea will target the small bowel, resulting

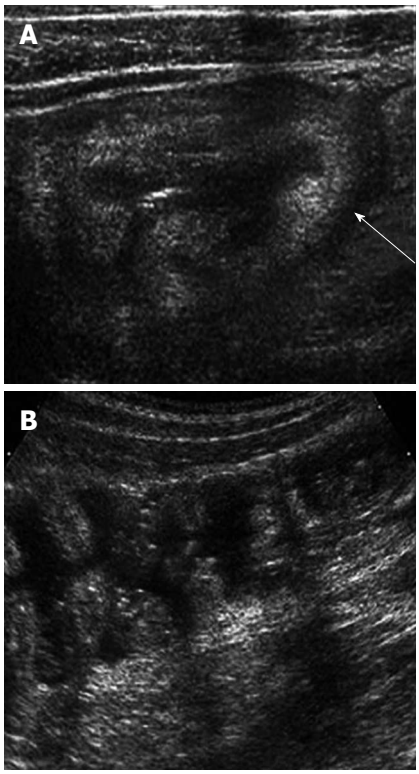

Figure 6 Bacterial enteritis. A: Ultrasound showing marked wall thickening of the cecum (arrow) in a child with right lower quadrant pain, which returned to normal; B: 4 d later. Stool cultures were positive for enterohemorrhagic *Escherichia coli*.

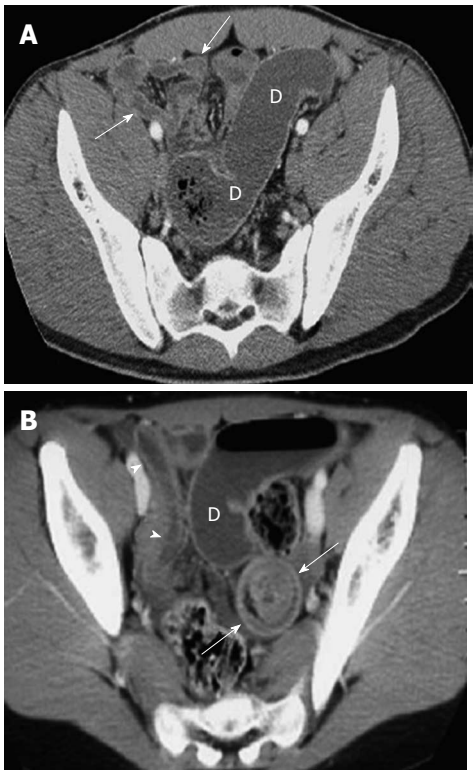

Figure 7 Meckel's diverticulum. A: Small-bowel obstruction shown on computed tomography (CT) in an 18-year-old boy with pathologically proven Meckel's diverticulum; B: CT image in an 11-year-old girl shows intussusception (arrows) as a bowel loop containing alternating rings of attenuation. Note dilated proximal small bowel (D) and collapsed terminal ileum (arrowheads).

in mid-abdominal cramping and large volumes of watery diarrhea. Bacterial diarrhea will target the large bowel, resulting in lower abdominal pain and smaller volumes of bloody mucoid diarrhea. Other diagnoses need to be considered when a child presents with vomiting, such as urinary tract infection, appendicitis, inborn errors of metabolism or volvulus, especially in very young infants, diabetic ketoacidosis and hemolytic uremic syndrome (the appearance of illness in children usually is preceded by diarrhea).

Plain radiographs are often normal but may show mild dilatation of small and large bowel. US is helpful in gastroenteritis to exclude other emergencies such as acute appendicitis or intussusception. US may show fluid-filled hyperperistaltic loops of bowel with little or no wall thickening in patients with gastroenteritis (Figure 6). However, abdominal CT scan is seldom used in patients with AGE except for cases with acute abdomen caused by AGE, such as septic peritonitis caused by bowel perforation.

Meckel's diverticulum

Meckel's diverticulum is defined as incomplete closure of the intestinal end of the omphalomesenteric duct that disappears normally by the seventh week of gestation. It is a true diverticulum, containing all layers of the bowel wall, and up to 60% of these diverticula contain heterotopic gastric tissue and heterotopic pancreatic, endometrial and duodenal mucosa[13,14]. It is the most common congenital gastrointestinal tract anomaly and affects 2% of the population. In addition, it is more common in males than females, with a male-to-female ratio of two to four and with the lifetime complication rate of about 4%[4]. The features of Meckel's diverticulum are commonly described by "the rule of 2s": it is present in approximately 2% of the population, with only 2% of affected patients becoming symptomatic. Forty-five percent of symptomatic patients are under 2 years of age. The most common location is 40 to 100 centimeters from the ileocecal valve and the diverticulum typically is about 5 cm long[15].

The classical presentation of Meckel's diverticulum is painless or minimally painful rectal bleeding. Such painless bleeding is a result of heterotopic gastric tissue in the diverticulum or the adjacent ileum. Abdominal pain, distension and vomiting may occur if obstruction has occurred and the clinical presentations may mimic appendicitis or diverticulitis. Meckel's diverticulum may also ulcerate and perforate, presenting as a bowel perforation, or act as a lead point, resulting in intussusception.

Abdominal films may show signs of obstruction, such as dilated loops of bowel or a paucity of bowel gas. A scan of Meckel's diverticulum can detect the presence of gastric mucosa within the diverticulum with up to 85% accuracy. Meckel's diverticulum may show one

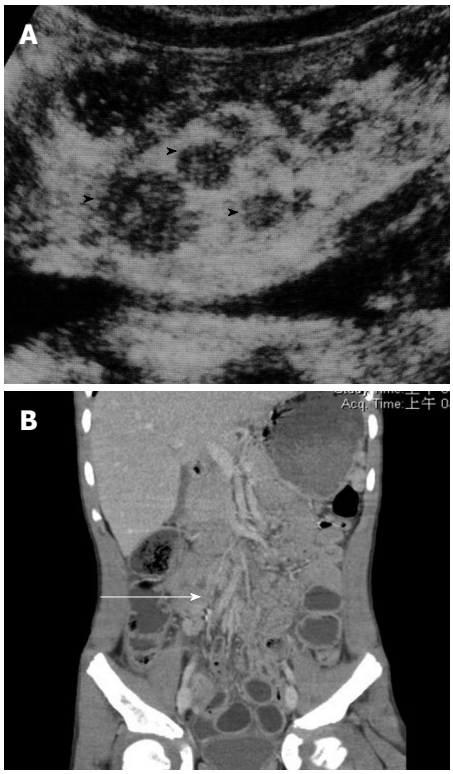

Figure 8 Mesenteric adenitis. A: Ultrasound shows multiple enlarged lymph nodes (arrowheads) at the base of mesentery, anterior to the inferior vena cava; B: Computed tomography of the abdomen showing clustering of mesenteric lymph nodes with largest diameter of about 11.2 mm (black arrow) and thickening of the bowel wall of terminal ileum.

of following patterns of presentations on CT: isolated small-bowel obstruction; intussusception with small-bowel obstruction; or a cystic mass with surrounding inflammatory changes (Figure 7)[15]. However, calcifications are not a common feature of CT for the diagnosis of Meckel's diverticulum.

A Tc-99m scan is the gold standard but is a less-sensitive tool for making a diagnosis preoperatively. Repeated Tc-99m scans in highly suspected cases and RBC scans in continuous bleeding patients improves the detection rate.

Mesenteric adenitis

In 1926, Wilensky and Hahn classified mesenteric lymphadenitis into four groups: Group Ⅰ: Simple mesenteric lymphadenitis; Group Ⅱ: Suppurative mesenteric lymphadenitis; Group Ⅲ: Tuberculous mesenteric lymphadenitis; and Group Ⅳ: Terminal stage of mesenteric lymphadenitis (calcification). It can, however, cause severe consequences and may at times be fatal. The severe form of this disease with suppuration, abscess formation and peritonitis is rare. Mesenteric adenitis is usually a self-limiting clinical condition characterized by fever, nausea, vomiting, diarrhea, diffuse or right lower quadrant abdominal pain and tenderness, and frequent leukocytosis. The causes of mesenteric adenitis have been reported to be viral, bacterial and mycobacterial infections. Numerous bacteria have been demonstrated to be involved in mesenteric nodes: *B. coli, staphylococci, streptococci, pneumococci, typhoid, paratyphoid* and *tubercle bacilli*.

Due to the clinical presentation of the abdomen, it could be difficult to discriminate this condition from other acute abdominal diseases such as acute appendicitis. Imaging examinations, such as an abdominal CT scan, can be a valuable tool in accurately diagnosing mesenteric adenitis and can help to avoid normal appendectomy due to the clinical misdiagnosis of appendicitis. Findings of mesenteric adenitis on CT include: (1) cluster of > 3 lymph nodes in RLQ mesentery with > 5 mm in short axis diameter; (2) normal appendix; (3) ileal wall thickening; and (4) colonic wall thickening (Figure 8)[16,17].

CONCLUSION

The etiologies of acute abdomen in children admitted to the emergency department vary depending on the age. A complete history and detailed physical examination, as well as abdominal imaging examinations, could provide useful information for physicians in the emergency department in order to narrow the differential diagnosis of abdominal emergencies and give a timely treatment.

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CASE REPORT

Midline synovial and ganglion cysts causing neurogenic claudication

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Abstract

Typically situated posterolateral in the spinal canal, intraspinal facet cysts often cause radicular symptoms. Rarely, the midline location of these synovial or ganglion cysts may cause thecal sac compression leading to neurogenic claudication or cauda equina syndrome. This article summarizes the clinical presentation, radiographic appearance, and management of three intraspinal, midline facet cysts. Three patients with symptomatic midline intraspinal facet cysts were retrospectively reviewed. Documented clinical visits, operative notes, histopathology reports, and imaging findings were investigated for each patient. One patient presented with neurogenic claudication while two patients developed partial, subacute cauda equina syndrome. All 3 patients initially responded favorably to lumbar decompression and midline cyst resection; however, one patient required surgical stabilization 8 mo later. Following the three case presentations, we performed a thorough literature search in order to identify articles describing intraspinal cystic lesions in lateral or midline locations. Midline intraspinal facet cysts represent an uncommon cause of lumbar stenosis and thecal sac compression. Such entities should enter the differential diagnosis of midline posterior cystic lesions. Midline cysts causing thecal sac compression respond favorably to lumbar surgical decompression and cyst resection. Though laminectomy is a commonly performed operation, stabilization may be required in cases of spondylolisthesis or instability.

Key words: Midline; Synovial; Ganglion; Intraspinal; Cyst; Neurogenic; Claudication; Laminectomy; Facet

Core tip: Midline, intraspinal cysts arise from facet joint degeneration. The lesions represent an important and often over-looked cause of back pain and other neurological symptoms. Radiographic identification of the fluid-filled sacs is particularly important in the setting of cauda equina syndrome, in which immediate surgical intervention is required in order to address the compressive lesion. Although the treatment of choice is a spinal decompression and resection, posterior fusions may prevent cyst recurrence.

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INTRODUCTION

Intraspinal facet cysts, also known as synovial and/or ganglion cysts, typically reside adjacent to the facet joints

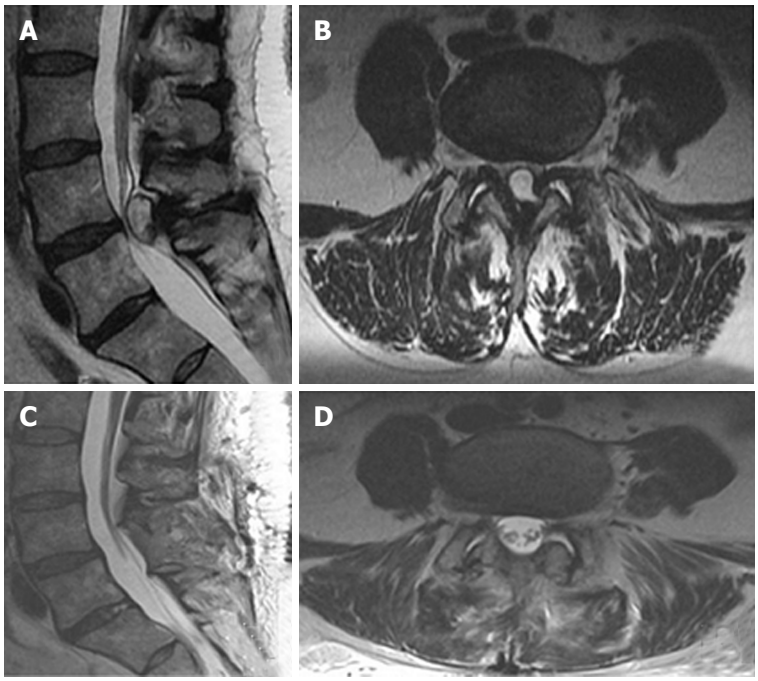

Figure 1 T2-weighted imaging of case 2. A, B: In the preoperative images, sagittal (A) and axial (B) T2 weighted magnetic resonance imaging displays a large intraspinal cystic lesion at the L4-5 level causing stenosis and thecal sac compression. The cystic lesion appears to have an eccentric component extending towards the left facet joint; C, D: Post-operative imaging following decompressive laminectomy and cyst excision. Bilateral laminectomies at L4-5 and cyst resection provide adequate decompression of the dorsal thecal sac and cauda equina, as shown in sagittal (C) and axial (D) images.

and may cause radicular symptoms due to nerve root compression and foraminal compromise. Representing a zygapophyseal joint, facet joints lie enclosed within a capsule lined by synovial epithelium[1]. Breakdown of this articular lining or encapsulated accumulation of fluid outside of the facet joint may lead to pathologic cyst formation. Synovial and ganglion cysts typically occur in the lower lumbar region, frequently the site of degenerative changes and dynamic instability[1-5]. They are found in the postero-lateral region of the canal, consistent with their source of pathology. Lined with cuboidal epithelium and filled with synovial fluid, synovial cysts frequently retain communication with their facet joint of origin[4,6]. In contrast, ganglion cysts lack synovial lining and structural communication to facet joints[3,6]. Ganglion cysts contain a collagenous or fibrous wall encircling gelatinous or myxoid substance[4,7-9]. Clinically, however, both terms are used interchangeably to describe intraspinal facet cysts or juxtafacet cysts[2-4,7,9]. This article presents 3 unique cases of midline intraspinal facet cysts causing significant lumbar stenosis and symptomatic thecal sac compression.

Three patients with symptomatic midline intraspinal facet cysts were reviewed. Clinical visits, operative notes, histopathology reports, and imaging findings were investigated for each patient. A thorough literature search was used to identify case reports or series describing intraspinal cystic lesions.

CASE REPORTS

Case 1

A 65-year-old woman presented with a 1-mo history of bilateral buttock pain and lower extremity weakness. The patient had full strength in her upper extremities and 4/5 strength in her proximal lower extremities. Magnetic resonance imaging (MRI) showed a grade 1 anterior listhesis of L4 on L5 as well as a well-circumscribed midline synovial cyst posterior to the thecal sac at the L4-L5 level; the hyperintense lesion on T2 weighted sequences measured approximately 8 mm × 8 mm × 10 mm. Differential diagnosis includes perineural (Tarlov) cysts, arachnoid cysts, and migrated disc fragment. The patient underwent bilateral laminectomies at L4-L5, bilateral foraminotomies, medial facetectomies, and cyst resection. Smaller cysts were encountered at the bilateral L4-L5 and the right L5-S1 facet joints. Histologic sections of the excised midline cyst revealed fragments of dense connective tissue with overlying synovium. The patient had an uncomplicated post-operative course and remained asymptomatic at 15-mo follow up.

Case 2

A 57-year-old woman presented with a 3-mo history of lower back, left lower extremity radiculopathy in the L5 and S1 distributions, and urinary incontinence. She exhibited full strength in the bilateral upper and lower extremities, with an unremarkable sensory exam. MRI revealed a large midline, well-circumscribed cystic lesion at the L4-L5 level, causing significant compression of the thecal sac and cauda equine; however, the images were unremarkable for spinal instability (Figure 1A and B). The patient underwent L4-L5 bilateral decompressive laminectomies with bilateral foraminotomies and cyst resection. Intraoperatively, a large intraspinal extradural cystic lesion appeared centrally, exerting significant compression on the thecal sac. While gross inspection revealed a cystic lesion containing clear viscous fluid, absence of epithelium lining the cystic cavity microscopic examination confirmed the final diagnosis of a ganglion cyst (Figure 2). The patient did well post-operatively. Imaging confirmed total cyst resection and adequate decompression of the thecal sac (Figure 1C and D). The patient

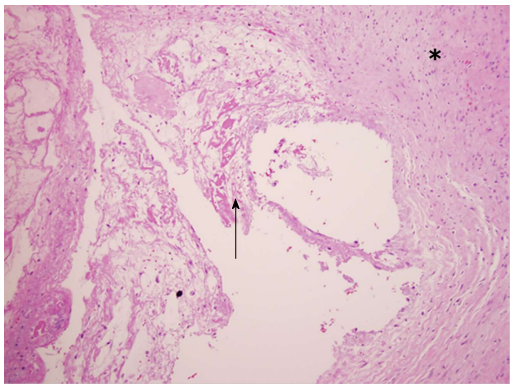

Figure 2 Case 2, pathological findings of midline ganglion cyst (hematoxylin eosin staining, × 400). Photomicrograph (original magnification × 400) reveals proteinaceous material (arrow) surrounded by dense fibro-connective tissue (asterisk), without the presence of synovial epithelium. These findings confirm the diagnosis of a ganglion cyst.

reported improvement in all symptoms, including urinary incontinence, at her latest follow-up 17-mo post-operatively.

Case 3

A 70-year-old woman presented with a 1-mo history of bilateral buttock and lower extremity pain. The patient denied bowel or bladder incontinence. On examination, she was neurologically stable. MRI revealed multilevel lumbar spondylosis as well as a large multiseptated cystic lesion appearing centrally and dorsolaterally in the L4-L5 extra-dural space with subsequent severe canal stenosis, without foraminal compromise. The patient underwent with bilateral L3-L5 laminectomies, medial facetectomies, and cyst resection. Gross inspection of the excised midline lesion revealed a cystic structure. Histologic examination of specimen permanent sections was consistent with a ganglion cyst. The patient had an uncomplicated post-operative course. A post-operative MRI demonstrated complete removal of the ganglion cyst with posterior decompression from L3-L5. The patient remained well until 3 mo after surgery when she developed low back, right buttock, and right anterior thigh pain. Epidural and facet injections were tried without symptomatic relief. Given the findings of junctional stenosis at L2 and mechanical instability suggested by imaging and clinical evaluation, the patient underwent L2-L5 bilateral, instrumented fusion eight months later. At last follow-up, the patient was completely asymptomatic (total follow-up period: 15 mo).

DISCUSSION

Juxtafacet cysts may reside deep or superficial to the posterior elements of the vertebral canal, or have a bi-lobed architecture existing in both compartments[7]. Intraspinal facet cysts usually neighbor degenerated facet joints in the postero-lateral epidural space[1-3,5,7,10]. The cysts most frequently occur at L4-L5, the lumbar level characterized by greatest mobility and prevalence of degenerative disease[4,7,9,11-13].

Imaging characteristics of intraspinal facet cysts vary depending on cyst content. Computed tomography (CT) typically portrays a well circumscribed hypodense lesion with hyperdense rim due to calcification[9,10]. MRI typically shows hyperintense cystic extradural lesions. The cysts appear centrally iso- to hyperintense compared to cerebrospinal fluid (CSF) and iso- to hypointense compared to soft tissue on T1 weighted sequences[1,4,6,7,10,14]. Facet arthropathy and degenerative spondylosis frequently accompany juxtafacet cysts on CT or MRI[2,3,7,9,10].

Clinically indistinguishable, histopathologic analysis distinguishes synovial from ganglion cysts. The presence of cuboidal synovial epithelium encircling synovial fluid corroborates the diagnosis of a synovial cyst. In contrast, the absence of synovial epithelial lining or the presence of chronic fibrotic tissue along the cavity wall supports the diagnosis of a ganglion cyst[4,7,8,11].

Several mechanisms have been described to explain the development of juxtafacet cysts. Ganglion cysts most likely result from cystic or myxoid degeneration of connective tissue. The most likely mechanism of synovial cyst formation involves degenerative articular changes due to abnormal and increased motion at the facet joint[4,6,9,11]. Several studies have described associations between spinal instability or degenerative changes, reflected by lumbar spondylosis or spondylolisthesis, and intraspinal facet cysts[11,12]. Acquired defects in the joint capsule allow protrusion of synovial epithelium and cyst formation adjacent to the joint; hence, the communication between degenerated facet joints and synovial cysts found in many cases[4,9]. Furthermore, juxtafacet cysts occur most frequently at the level of greatest motion and prevalence of degenerative changes, L4-5, followed by L5-S1 and L3-4[4,9,11-13].

In the absence of neurologic deficits, symptomatic patients with intraspinal facet cysts may benefit from conservative management. Non-surgical treatments include activity restrictions, supportive bracing, oral analgesics or anti-inflammatories, physical therapy, and epidural or facet steroid injections[7,11,12]. Minimally invasive procedures include percutaneous injection or cyst aspiration[4,11,12]. However, failure of conservative measures has been widely documented by several clinical series[6,10-12]. Standard surgical techniques include hemilaminotomy or laminectomy, foraminotomy, medial facetectomy, and cyst excision[2,4,6,10-12].

Most clinical series demonstrate moderate to high rates of successful outcomes in patients undergoing decompressive surgery with juxtafacet cyst resection[6,10,12]. Epstein reported good to excellent results in 58%-63% of patients undergoing decompressive surgery for synovial cysts and accompanying stenosis, with or without spondylolisthesis[10]. Most other clinical series report similar or even higher rates of favorable outcomes[10]. In their meta-analysis, Bydon *et al*[12] reported short-term post-operative resolution of back and lower extremity pain in above 90% of patients compiled. In prolonged follow-up, nearly 22% and 13% of patients reported recurrent back pain and radiculopathy, respectively. Delayed surgical complications include intraspinal facet cyst recurrence

and the development or progression of spinal mechanical instability[11,12]. Static or dynamic imaging may reveal low grade spondylolisthesis or minimal instability in a minority of asymptomatic patients[6].

In the present case series, one patient demonstrated clinical and radiographic evidence of post-operative spinal instability and required an instrumented fusion at 8 mo follow-up. Such outcomes speak to the role of spinal fusion as an adjunct to decompression and cyst excision given the likely role of facet joint hypermobility and degeneration in the pathophysiology of synovial cyst formation[10-13]. While potentially improving mechanical back pain, concomitant spinal fusion may limit further destabilization and prevent cyst recurrence[6,11-13]. Although current studies reflect the predominance of decompression and cyst excision without fusion in the majority (> 80%) of surgical cases for synovial cysts[12], patients with clinical and radiographic evidence of post-operative spinal instability may benefit from concomitant surgical fixation and/or fusion[6,10-12]. Some authors suggest that radiographic indications for pre-operative spinal instability, such as spondylolisthesis, are the strongest predictor for post-operative instability, especially after spinal decompression[15-19]. However, patients without pre-operative spondylolisthesis may still develop post-operative spinal instability requiring a fusion, as demonstrated in case number three. Furthermore, same level cyst recurrence occurred in nearly 2% of patients, all following decompression and cyst resection alone. In contrast, cyst reformation did not occur in any patients following concomitant spinal fusion[12]. These findings stress the importance of considering concomitant spinal fusion with decompression and synovial cyst excision.

Lessons learned from this case series in that despite their rare occurrence, midline synovial and ganglion cysts should be considered in the differential diagnosis of centrally located posterior extradural cysts. When causing symptomatic lumbar stenosis and thecal sac compression, midline synovial and ganglion cysts may require decompressive laminectomy and resection to relieve patients' symptoms and restore neurologic function. In the setting of baseline back pain or radiographically proven mechanical instability, concomitant spinal fusion may be considered. Following decompression and cyst excision alone, patients should be monitored closely for the progression or development of mechanical instability.

In this manuscript, we present a unique presentation of symptomatic, intraspinal cysts. Following the cyst recurrence, lumbar fusion may prevent long-term spinal instability or cyst recurrence. However, we do recognize that our manuscript is a limited case series of three patients. Larger cohorts are required to delineate the clinical outcomes in patients with midline synovial and ganglion cysts.

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COMMENTS

Case characteristics

Three patients with symptomatic midline intraspinal facet cysts were retrospectively reviewed. Documented clinical visits, operative notes, histopathology reports, and imaging findings were investigated for each patient.

Clinical diagnosis

One patient presented with neurogenic claudication while two patients developed partial, subacute cauda equina syndrome.

Differential diagnosis

All 3 patients initially responded favorably to lumbar decompression and midline cyst resection; however, one patient required surgical stabilization 8 mo later.

Imaging diagnosis

Radiographic identification of the fluid-filled sacs is particularly important in the setting of cauda equina syndrome, in which immediate surgical intervention is required in order to address the compressive lesion.

Treatment

All 3 patients initially responded favorably to lumbar decompression and midline cyst resection; however, one patient required surgical stabilization 8 mo later.

Related reports

Some authors suggest that radiographic indications for pre-operative spinal instability, such as spondylolisthesis, are the strongest predictor for post-operative instability, especially after spinal decompression

Experiences and lessons

The authors present a unique presentation of symptomatic, intraspinal cysts. Following the cyst recurrence, lumbar fusion may prevent long-term spinal instability or cyst recurrence.

Peer review

This manuscript illustrates a unique presentation, location, and management of intraspinal cysts. The article is well-written and does not require modifications.

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CASE REPORT

Tissue plasminogen activator *via* cross-collateralization for tandem internal carotid and middle cerebral artery occlusion

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Abstract

Tandem internal carotid and middle cerebral artery occlusion after carotid dissection predicts poor outcome after systemic thrombolysis. Current treatments include the use of endovascular carotid stenting, which carries with it a high risk of propagating further embolic events and worsening the dissection. New strategies for avoiding the aforementioned side-effects include recanalization using cross-collaterals for delivery of intra-lesional tissue plasminogen activator (tPA). We present two cases that provide further support for this novel approach. Both patients presented with a National Institute of Health Stroke Scale of 20, received intra-arterial tPA *via* cross-collateralization, and made full recoveries without the need for stenting.

Key words: Tandem internal carotid artery and middle cerebral artery occlusion; Intra-arterial tissue plasminogen activator; Carotid artery dissection

Core tip: Tandem internal carotid artery and middle cerebral artery occlusions secondary to carotid artery dissections are refractory to stand alone medical management and often result in poor outcomes in patients receiving systemic tissue plasminogen activator (tPA). Cervical carotid stent assisted endovascular thrombolysis is effective, but carries the risk of worsening the dissection and propagating further thromboembolic events. Avoidance of carotid occlusions and recanalization with intra-arterial tPA using cross-collateralization, may be an effective, alternative treatment for patients with tandem internal carotid artery and middle cerebral artery occlusions.

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INTRODUCTION

Dissection of the internal carotid artery (ICA) accounts for a significant proportion of ischemic stroke in young patients, representing up to a quarter of such cases[1,2]. Lucas and colleagues illustrated that the underlying pathophysiology of carotid artery dissection ischemia is most often due to thrombus formation and secondary embolization[3]. In many cases, this embolization can result in a tandem ICA and middle cerebral artery occlusion (TIM)[4]. At presentation, patients with TIM occlusions usually have a similar clinical severity to those with isolated middle cerebral artery (MCA) obstruction. However, they have a lower chance of MCA recanalization

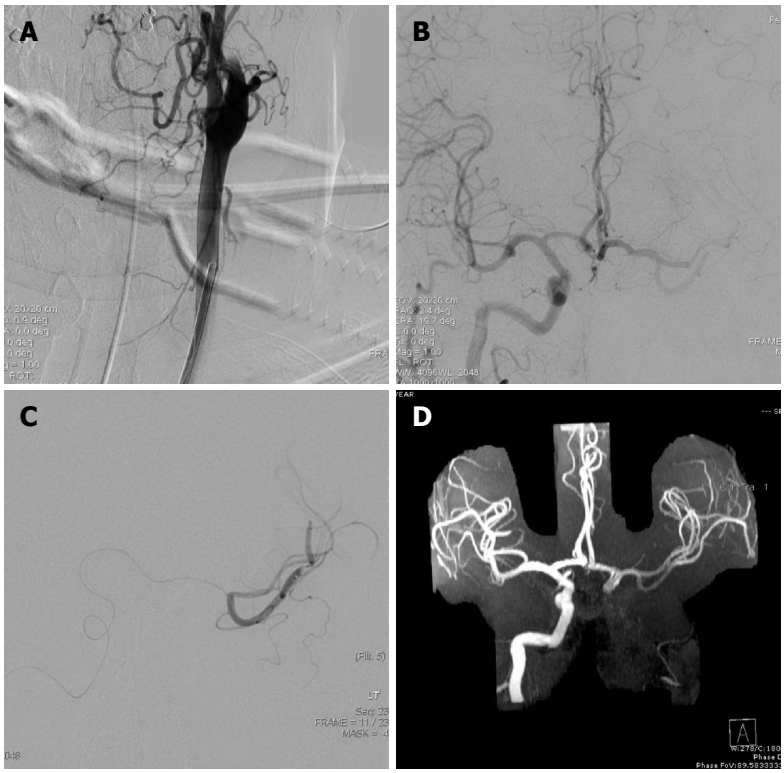

Figure 1 Pre and post intervention cerebral angiography. A: Left carotid occlusion from likely dissection; B: Cross filling of the left internal carotid artery distribution *via* right internal carotid artery injection. The left middle cerebral artery (MCA) distribution does not completely opacify due to thrombus; C: Microcatheter crossing into the left MCA *via* the anterior communicating artery. Intra-arteria tissue plasminogen activator was delivered; D: Magnetic resonance angiography performed 10 h later confirms patency of the left MCA branches correlating with the patient's resolution of clinical symptoms.

after systemic tissue plasminogen activator (tPA) therapy and often result in worse clinical outcomes[4-6]. A review of 221 stroke patients identified TIM occlusions as an independent predictor of poor outcomes after systemic thrombolysis[6].

The current treatment regime involves systemic tPA within 3 h of presentation. However, as previously noted, this may not allow adequate cerebral reperfusion in a TIM occlusion and may, unfortunately, predispose the development of a malignant brain infarct[7]. In order to improve clinical outcomes, this group of patients may need more aggressive intervention to restore cerebral perfusion. However, the ideal treatment for such cases remains elusive[8,9].

Recently, treatment of patients with ICA dissections refractory to medical management has focused on endovascular stenting and angioplasty[10]. A small patient series described stent-assisted thrombolysis in TIM occlusions. Specifically, the proximal ICA was recanalized with stent implantation followed by MCA recanalization *via* subsequent intra-arterial thrombolysis or thrombectomy[11]. In theory, endovascular therapies in the treatment of carotid dissection occlusions may lead to significant procedural complications, as the lesion pathology requires the interventionist to navigate the true lumen. Failure to do so may result in extending the dissection or vessel perforation, which in turn may lead to worse outcomes.

In certain cases, avoidance of the ICA may be preferred. Treatment of the MCA occlusion in a TIM by bypassing the ICA has only been described in three previous reports[12-14]. We provide two additional cases demonstrating the successful recanalization of an MCA occlusion by administering intra-arterial tPA through a microcatheter guidewire *via* cross-collateralization.

CASE REPORT

A 52-year-old male arrived at an outside hospital with global aphasia, right hemiplegia and a National institute of Health Stroke Scale (NIHSS) of 20. He was found to have a left MCA stroke on head computed tomography (CT). Tele Stroke was activated and he was given intravenous (*iv*) tPA at 1.5 h after symptom onset and transferred to a tertiary hospital. The patient's exam remained unchanged on arrival, head CT showed no evidence of stroke, and he was subsequently taken to the angiography suite.

Under general anesthesia, the left common carotid artery was catheterized and images of the cervical carotid arteries were obtained (Figure 1A). He was found to have a left carotid artery dissection (CAD). At this point, the proximal left ICA was partially opened. The true lumen, however, was difficult to identify and further attempts risked propagating the dissection intracranially.

Subsequently, the right ICA was catheterized through the right common carotid artery for angiography. A thrombus was located in the middle Sylvian (M2) position; imaging was obtained during the arterial phase so opacification was not seen. The anterior communicating artery (ACOMM) was slightly greater than 1 mm. At this point, a microcatheter was advanced from the right internal carotid system *via* the ACOMM into the left MCA. Both the superior and inferior trunks were catheterized and a total of 2 mg of tPA was delivered in each trunk providing an additional 4 mg to the systemic tPA dose (Figure 1B and C).

Post-procedure Thrombolysis in Cerebral Infarc-

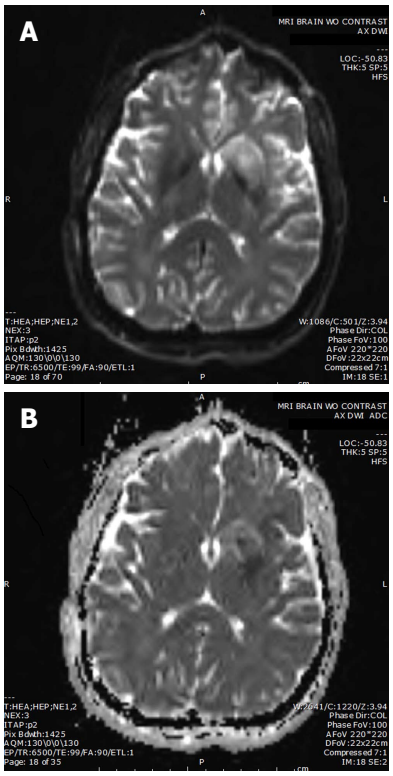

Figure 2 Ten hours post procedure imaging demonstrating small left subcortical infarct. A: Post procedure diffusion weighted magnetic resonance imaging; B: Post procedure apparent diffusion coefficient.

tion (TICI) score and immediate arteriogram were unchanged. The intervention was performed three hours post symptom onset and the procedure duration was two hours. Ten hour magnetic resonance angiography (MRA) confirmed recanalization of the MCA (Figure 1D), and magnetic resonance imaging (MRI) revealed a small stroke (Figure 2). Pre-procedure MRI was not performed. Heparin (*iv*) was given on the following day. Of note, anticoagulation was not started earlier since the patient received a full dose of *iv* tPA prior to the intervention. After twenty-four hours, the patient had full strength and minimal word finding with an NIHSS of two. After 3 mo, his NIHSS was zero. Three years later, he has returned to work and continues without neurological deficits.

Our second patient was a 40-year-old male who presented with left hemiplegia, and was diagnosed with CAD after obtaining a cerebral angiogram. He was treated with intra-lesional tPA *via* cross-collateralization, and recanalization of the right MCA was obtained eight hours post presentation. His pre and post-procedure NIHSS, as well as his NIHSS 3 mo later, were by coincidence the same as the first patient. He continues to have a non-focal neurologic exam three years post treatment.

DISCUSSION

Ischemic stroke associated with CAD is primarily due to embolic phenomena, which can affect many vessels and commonly targets the ICA, MCA or both in tandem. The latter independently predicts poor clinical outcome and so efficacious and consistent treatments are highly desired[6]. Thrombolysis has typically been the management of choice for CAD, and is thought to prevent subsequent embolic events[15]. However, a definitive treatment of choice for CAD does not exist. Evidence for tPA use in CAD is lacking, and may be associated with certain risks including hematoma extension and subarachnoid hemorrhage. Thrombolytics (*iv*) have been shown to cause recanalization in approximately 30%-40% of patients. This treatment has not been efficacious in the case of TIM[6]. Of interest, endovascular stenting has successfully been employed to treat medical refractory CAD that resulted in thromboembolic events[11,16].

Lavallée *et al*[11] analyzed the benefits of stent assisted endovascular thrombolysis with *iv* tPA involving a small series of ICA dissections. In this study, 10 patients who met the selection criteria were given either systemic tPA (n = 4) or endovascular stenting and intra-lesional tPA (n = 6). Those in the endovascular group had significantly better prognosis, which was linked to recanalization of the occluded vessels, particularly the MCA. The MCA was patent in all endovascular cases and occluded in three of the four cases in the systemic tPA group. Both embolization and in stent thrombosis were side effects of endovascular treatment.

Opening the ICA is the ideal option, however, given the difficulty of observing the true carotid lumen and associated risk of extending the dissection intracranially, bypassing the dissection was considered the optimal strategy. Rahme *et al*[13] describes 15 cases in the literature of treating MCA thrombosis in TIM occlusions *via* cross-collateralization, and recanalization was achieved in 54.5%-75.0% of cases. Our report provides further support for the strategy of treating TIM occlusion *via* delivery of intra-lesional tPA using collateral vessels. In both cases presented, intra-lesional tPA was administered through a microcatheter passed through the ACOMM, and recanalization was observed *via* angiographic improvement on MRA. At 3 mo, both patients had fully recovered and returned to their daily activities. They continued to have a non-focal neurologic exam three years later.

Our presented cases did not have any complications, however, the risk of the described intervention includes endangering the contralateral carotid circulation, damaging smaller collateral arteries, and compromising collateral flow. Specifically, instrumenting small caliber arteries may result in dissection, occlusion, or distal thrombosis. This approach is ideal for patients in whom it is felt that the cervical carotid artery cannot be safely recanalized or in whom recanalization of the cervical carotid artery may lead to significant reperfusion hemorrhage. The ideal patient for this procedure is directly dependent on the presence of a collateral vessel, like the ACOMM, having an adequate diameter for passage of a microcatheter. Radiographic studies have demonstrated that an intact anterior circulation is present in 74%-90% of the population and

an intact posterior circulation is present in 48.5%-63% of the population[17-20]. Of note, a review of anatomic variants in healthy Chinese individuals demonstrated that a complete anterior circulation with incomplete posterior circulation is present in 47.7% of individuals; a complete posterior circulation with an incomplete anterior circulation is only present in 5.2% of individuals[17]. Another risk includes receiving an additional 4 mg of tPA to the systemic dose which increases risk for hemorrhage. It is important to analyze the risks and benefits of any procedure. The presented patients were highly functional with a devastating stroke, and, therefore, the intervention was considered worthwhile.

TIM secondary to CAD are refractory to pure medical management and strongly predict poor outcomes in patients. Stent assisted endovascular thrombolysis is effective when compared against traditional management but carries an additional risk of worsening the dissection and propagating further thromboembolic events. Therefore, avoidance of the occluded carotid artery may be preferred in certain scenarios. In these cases, delivery of intra-lesional tPA using collateral vessels resulted in complete clinical recovery and recanalization of the occluded MCA. Our experience provides further support for utilization of this novel method of treatment when other modalities may not be feasible.

COMMENTS

Case characteristics

Tandem internal carotid artery and middle cerebral artery occlusions secondary to carotid artery dissections are refractory to stand alone medical management, and recanalization with intra-arterial tissue plasminogen activator (tPA) using cross-collateralization may be an effective alternative for treating these patients.

Clinical diagnosis

The patient presented with global aphasia and right hemiplegia suggestive of a left middle cerebral artery stroke.

Differential diagnosis

The differential diagnosis includes left middle cerebral artery thrombosis or dissection.

Imaging diagnosis

Cerebral angiography revealed left internal carotid artery dissection and left middle cerebral artery occlusion.

Treatment

tPA (*iv*) was first used for recanalization but failed, therefore, catheter guided intra-arterial delivery of tPA was then implemented towards successfully recanalizing the middle cerebral artery occlusion.

Related reports

There have only been three reports describing the use of intra-arterial tPA delivery *via* cross-collaterals in the literature, and we provide two more cases supporting its use in treating tandem internal carotid artery and middle cerebral artery occlusions.

Term explanation

Cross-collateralization: Using collateral vessels to navigate endovascular instruments around abnormal or damaged vessels.

Experience and lessons

Stent assisted endovascular thrombolysis of tandem internal carotid artery and middle cerebral artery occlusions (TIM) is effective but carries the risk of worsening the dissection and propagating further thromboembolic events, and, therefore, avoidance of carotid occlusions and recanalization with intra-arterial tissue plasminogen activator, using collateral vessels may be an effective alternative for treating patients with TIM.

Peer review

The strengths of this article is that it provides additional cases where utilizing collateral vessels was an effective strategy for treating tandem internal carotid artery and middle cerebral artery occlusions. The report also summarizes important factors to consider when determining whether a patient is a good candidate for this intervention. The study is well-written and interesting.

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CASE REPORT

Intracranial hypotension syndrome in a patient due to suboccipital craniectomy secondary to Chiari type malformation

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Abstract

Intracranial hypotension syndrome (IHS) is a rare disorder characterized by a decrease in cerebrospinal fluid pressure to less than 60 mm H_2O. The syndrome is associated with occipital headache radiating to the frontal and temporal zones. The current clinical case describes the manifestation of IHS in a twenty-five year old female with a history of suboccipital craniectomy due to Chiari I malformation nine years earlier. The patient was admitted to the hospital complaining about postural, mainly occipital, headache during the last three months, aggravated by being in an upright position. The magnetic resonance imaging (MRI) revealed engorgement of the dural venous sinuses, significant enlargement of the pituitary gland and download displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern, while the spinal T2W MRI revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine. The previous imaging did not reveal subdural effusions.

Key words: Headache; Craniectomy; Cerebrospinal fluid; Intracranial hypotension syndrome; Effusion; Chiari

Core tip: A 25-year-old female presented with a history of suboccipital craniectomy due to Chiari I malformation nine years earlier. The patient was admitted to the hospital with symptoms of postural, mainly occipital, headache during the last three months, aggravated by being in an upright position. The spinal T2W magnetic resonance imaging revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine. The current clinical case indicates that a longer follow-up and increased alertness are required in a patient with a history of craniectomy due to Chiari I malformation.

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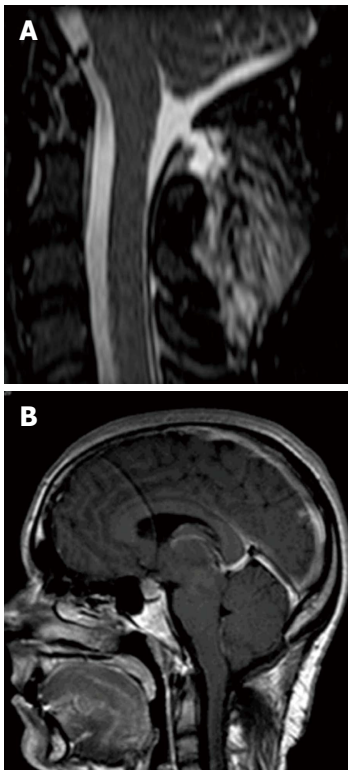

Figure 1 Magnetic resonance imaging signs of intracranial hypotension syndrome nine years after the craniectomy. A: 7 mm × 2.5 mm dural defect with an extradural collection at the dorsal soft tissues of the cervical spine; B: Less prominent engorgement of the dural venous sinuses, further enlargement of the pituitary gland and download displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern.

INTRODUCTION

Intracranial hypotension syndrome (IHS) is a rare disorder characterized by a decrease in cerebrospinal fluid pressure. IHS is associated with occipital headache similar to the orthostatic headache after lumbar puncture. They both radiate to the frontal and temporal zones and are aggravated in an upright position. HIS is also characterized by dural thickening and pachymeningeal contrast enhancement as a consequence of decreased cerebrospinal fluid (CSF) volume. Although spinal cerebrospinal fluid leaks may be the cause of this syndrome, only a few clinical or radiological cases have been reported.

CASE REPORT

A 25-year-old female presented with a history of suboccipital craniectomy due to Chiari I malformation 9 years earlier. The patient was admitted to the hospital complaining about postural, mainly occipital, headache during the last three months. The headache was aggravated by being in an upright position. The magnetic resonance imaging (MRI) revealed mild engorgement of the dural venous sinuses, significant enlargement of the pituitary gland and download displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern (Figure 1B), while the spinal T2W MRI revealed a 7 mm × 2.5 mm dural defect with an extradural CSF collection at the dorsal soft tissues of the cervical spine (Figure 1A). The postoperative MRI nine years earlier revealed significant engorgement of the dural venous sinuses and mild enlargement of the pituitary gland without signs of download displacement or sagging of the brain (Figure 2). Even although the previous imaging did not reveal subdural effusions, the postoperative MRI revealed signs of intracranial hypotension syndrome soon after the suboccipital craniectomy. Nevertheless, the typical clinical symptoms of IHS only manifested three months before the admission of the patient. During the postoperative follow-up, the patient complained of intermittent occipital headaches, mostly explained by the Chiari malformation.

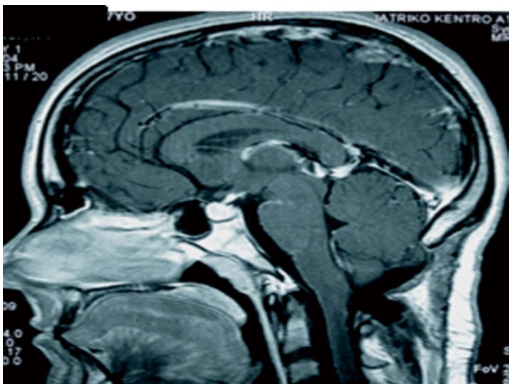

Figure 2 Magnetic resonance imaging signs of intracranial hypotension syndrome postoperatively. There is significant engorgement of the dural venous sinuses and mild enlargement of the pituitary gland without signs of download displacement or sagging of the brain.

DISCUSSION

IHS is a rare disorder with a prevalence of about 1 per 50000 population[1]. The latest studies indicate that the estimated incidence is higher because the disorder remains under recognized[2]. This rare syndrome is characterized by a decrease in cerebrospinal fluid pressure to less than 60 mm H_2O. IHS is associated with occipital headache radiating to the frontal and temporal zones, dural thickening and pachymeningeal contrast enhancement as a consequence of decreased CSF volume. The 5 characteristic imaging features of spontaneous intracranial hypotension visible on MRI are: (1) subdural fluid collections; (2) enhancement of the pachymeninges; (3) engorgement of venous structures; (4) pituitary hyperemia; and (5) sagging of the brain (mnemonic: SEEPS)[3]. Headache due to IHS is similar to the orthostatic headache after lumbar puncture. They both are aggravated in an upright position. ISH is highly related to a spontaneous CSF leak. In most cases, spinal cerebrospinal fluid leaks are related to the pathogenic mechanism of the syndrome. Nevertheless, they have rarely been demonstrated radiographically or surgically[1]. Some of the spontaneous CSF leaks are related to weakness of the meningeal sac, likely

in connection with a connective tissue abnormality[4]. In clinical practice, the 2004 International Classification of Headache Disorders criteria cannot satisfy 100% of patients with HIS because of the variability of clinical and radiological manifestations[5]. Furthermore, although both intracranial hypotension syndrome and Chiari I malformation have been well described, their simultaneous presence has rarely been reported[6]. The current case indicates that even although the patient's postoperative MRI revealed signs of IHS, the clinical features were intermittent and did not meet the IHS criteria. Therefore, a patient with a history of Chiari I malformation and intermittent occipital headache after craniectomy requires increased alertness and a longer follow-up.

COMMENTS

Case characteristics

A 25-year-old female presented with a history of suboccipital craniectomy due to Chiari I malformation nine years earlier.

Clinical diagnosis

The patient was admitted to the hospital complaining of postural, mainly occipital, headache during the last three months. The headache was aggravated in an upright position.

Imaging diagnosis

The magnetic resonance imaging (MRI) revealed engorgement of the dural venous sinuses, significant enlargement of the pituitary gland and download displacement or sagging of the brain with effacement of the perichiasmatic cisterns and the prepontine cistern, while the spinal T2W MRI revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine.

Treatment

The spinal T2W magnetic resonance imaging revealed a 7 mm × 2.5 mm dural defect with an extradural cerebrospinal fluid collection at the dorsal soft tissues of the cervical spine.

Related reports

Latest studies indicate that the estimated incidence is higher because the disorder remains under recognized.

Experiences and lessons

A patient with a history of Chiari I malformation and intermittent occipital headache after craniectomy requires increased alertness and a longer follow- up.

Peer review

This clinical association is very rare and a larger number of patients are needed in order to have a wide clinical picture.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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Patent (list all authors)

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