

Xp11.2 易位/TFE3 基因融合相关性肾癌与 肾透明细胞癌差异性分析

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[摘要] 目的:从临床、影像、病理特点三方面比较 Xp11.2 易位/TFE3 基因融合相关性肾癌(Xp11.2 易位性肾癌)与肾透明细胞癌的差异性。方法:收集我院 2010 年 1 月~2015 年 12 月经手术治疗的肾癌患者 411 例,经病理证实 Xp11.2 易位性肾癌有 12 例,肾透明细胞癌有 302 例,就两组肾癌在临床、影像、病理特点进行分析。结果:Xp11.2 易位性肾癌 45 岁以下(83.3%)常见,发病年龄略低[Xp11.2 易位性肾癌患者平均年龄(33.1±18.4)岁,肾透明细胞癌患者平均年龄(63.1±11.2)岁],女性高发(66.7%),肉眼血尿首诊占 58.3%,查体首诊占 16.7%。肾透明细胞癌男性高发(66.6%),查体首诊占 55.9%,肉眼血尿首诊占 19.5%。CT:Xp11.2 易位性肾癌平扫密度稍增高,易出现点状钙化和不均质改变。增强扫描肿瘤动脉期、静脉期和延迟期 CT 值分别为(83.4±40.1)HU、(95.8±39.1)HU 和(80.4±30.1)HU。肾透明细胞癌平扫等密度或混杂密度,极少出现钙化,增强扫描肿瘤动脉期、静脉期和延迟期 CT 值分别为(133.4±37.1)HU、(102.8±19.1)HU 和(87.4±29.1)HU。MRI 扫描:Xp11.2 易位性肾癌 T1WI 病灶等信号,T2WI 低信号,肾透明细胞癌 T1WI 病灶等或高信号,T2WI 为不均匀混杂信号,增强扫描均呈渐进式延迟强化。病理特点:Xp11.2 易位性肾癌全部表达 TFE3 核蛋白,FISH 检测可确诊,肾透明细胞癌不表达 TFE3,FISH 阴性。两组肾癌患者术后随访 12~72 个月,中位随访时间(59.7±10.6)个月。Xp11.2 易位性肾癌术后发生转移者 4 例(33.3%),肾透明细胞癌患者 23 例(7.6%)。结论:Xp11.2 易位性肾癌多见于伴有肉眼血尿的年轻女性,增强 CT 表现为少进-慢出式强化,肾透明细胞癌中老年男性高发,多为查体发现,增强 CT 表现为快进-快出式强化,MRI 对两组肾癌的鉴别意义不大,最终诊断依据 FISH 检测。

[关键词] Xp11.2 易位;TFE3 基因融合;肾透明细胞癌;差异性

doi:10.13201/j.issn.1001-1420.2017.03.009

[中图分类号] R737.11 **[文献标识码]** A

Difference between renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusions and clear cell renal cell carcinoma

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Abstract Objective: To compare the difference between renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusions (Xp11.2 RCC) and clear cell renal cell carcinoma (CCRCC) in terms of clinical characters, imaging features and pathological traits. **Method:** From January 2010 to December 2015, 411 patients who were operated in Affiliated Hospital of Qingdao University were identified with renal carcinoma including 12 cases diagnosed as Xp11.2 RCC and 302 cases diagnosed as CCRCC. Clinical traits, imaging features and pathology characters were compared between the two groups. **Result:** Xp11.2 RCC often occurred in young patients [average age: Xp11.2 RCC (33.1±18.4); CCRCC (63.1±11.2) years old] whose clinical presentations were gross hematuria (58.3%) and examinations (16.7%) and below 45 years old (83.3%) whereas CCRCC often occurred in men patients (66.6%) whose clinical presentations were examination (55.9%) and gross hematuria (19.5%). CT of unenhanced scanning showed the lesions were slightly high density, and punctate calcifications and heterogeneous changes can be easily seen in part of the Xp11.2 RCC. Enhanced scanning showed the CT number of the arterial, venous and balance phases were (83.4±40.1) HU, (95.8±39.1) HU and (80.4±30.1) HU. On the aspect of CCRCC, unenhanced scanning showed equal or mixed density, but calcification was rare. Enhanced scanning showed the CT number of the arterial, venous and balance phases were (133.4±37.1) HU, (102.8±19.1) HU and (87.4±29.1)HU. MRI scanning showed T1WI of the Xp11.2 RCC was mediate signal, and T2WI low signal. T1WI of CCRCC was mediate or high signal, and T2WI was uneven signal. Enhanced scanning showed progressive delayed enhancement in all patients. Immunohistochemical exam illustrated that all Xp11.2 RCC were

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positive for TFE3, and it was confirmed by FISH. However, no TFE3 was positive in CCRCC. Four patients (33.3%) were diagnosed as distant metastasis after 12 to 72 months (59.7 ± 10.6) of follow-up period among Xp11.2 RCC. Twenty-three patients (7.6%) were diagnosed as distant metastasis among the CCRCC. **Conclusion:** Young women patients with hematuria usually occur in Xp11.2 RCC, and dynamic CT scanning shows low into-slow out strengthening. Elderly men with examination usually occur in CCRCC, and dynamic CT scanning shows fast into-fast out strengthening. Differential diagnosis depends on FISH rather than MRI.

Key words Xp11.2 translocation; TFE3 gene fusion; clear cell renal cell carcinoma; difference

肾细胞癌是源发于肾实质内小管上皮的恶性肿瘤,约占肾脏恶性肿瘤的80%~90%,肾透明细胞癌在肾癌中最常见,约占89.6%^[1]。Xp11.2易位性肾癌较少见,约占成年人肾癌的1.5%^[2],WHO在2004年肾细胞癌病理分类标准里将这一肾癌作为一种独立的亚型列出^[3]。因Xp11.2易位性肾癌发病率低,组织形态与肾透明细胞癌极为相似,再加上对这一亚型认识不足,没有统一的诊断标准,术前较难作出诊断。本文从临床、影像学、病理三方面综合评价两种肾癌,比较其差异性,提供诊断、循证医学参考依据。现报告如下。

1 资料与方法

1.1 临床资料

收集我院2010年1月~2015年12月经手术治疗的肾癌患者411例,其中经病理证实为Xp11.2易位性肾癌患者有12例(2.9%),肾透明细胞癌患者有302例(73.5%)。Xp11.2易位性肾癌组男5例,女7例;发病年龄4~67岁,平均年龄(33.1 ± 18.4)岁;首发症状为肉眼血尿7例(58.3%),查体发现2例(16.7%),腰痛1例(8.3%),其他原因2例(16.7%);术后随访发生转移4例(33.3%),失访2例。肾透明细胞癌组男201例,女101例;发病年龄23~81岁,平均年龄(63.1 ± 11.2)岁;查体发现169例(56.0%),首发症状为肉眼血尿59例(19.5%),腰痛52例(17.2%),其他原因22例(7.3%);术后随访发生转移23例(7.6%),失访19例。所选随访方案依据2015年欧洲泌尿外科学会肾细胞癌指南中的随访方案进行,至患者死亡随访终止。

1.2 方法

设计肾癌随访调查表,对患者一般情况分类统计,包括:姓名、性别、年龄、起病原因、病理类型、术后转移及治疗等情况。

1.3 影像学特点

分析314例肾癌患者的CT检查后我们发现,多数Xp11.2易位性肾癌平扫密度稍增高,易出现点状钙化、出血等不均质改变。增强扫描肿瘤动脉期、静脉期和延迟期CT值分别为(83.4 ± 40.1)HU、(95.8 ± 39.1)HU和(80.4 ± 30.1)HU,动脉期中等程度强化,静脉期持续强化,并在延迟期缓慢衰减,呈现出“少进-慢出”的强化类型(图1)。肾

透明细胞癌平扫等密度或混杂密度,极少出现钙化,增强扫描肿瘤动脉期、静脉期和延迟期CT值分别为(133.4 ± 37.1)HU、(102.8 ± 19.1)HU和(87.4 ± 29.1)HU,动脉期快速强化,静脉期快速衰减,延迟期继续衰减,典型“快进-快出”式强化(图2),肾透明细胞癌动脉期CT值明显高于Xp11.2易位性肾癌。MRI扫描,Xp11.2易位性肾癌T1WI病灶等信号,T2WI低信号,肾透明细胞癌T1WI病灶等(或)高信号,T2WI为不均匀混杂信号,增强扫描均呈渐进式延迟强化。

1.4 病理学特点

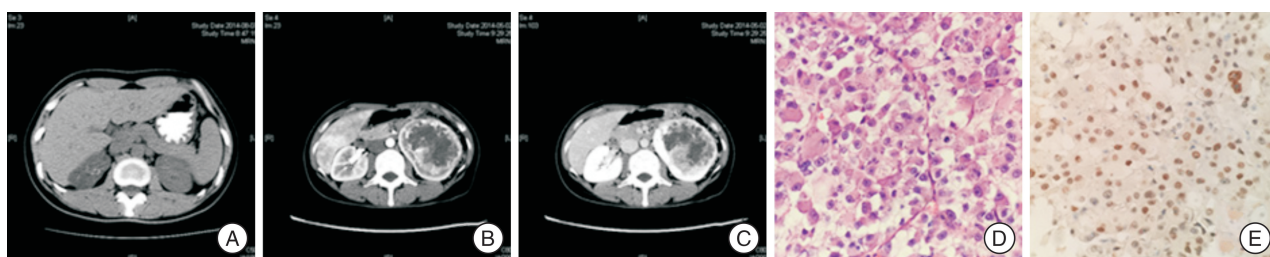
病理方面的差异主要依靠组织病理学和免疫组织化学。组织病理学方面,Xp11.2易位性肾癌同透明细胞癌相像,边界清楚,有假包膜,剖面多呈黄色,可见出血、坏死、囊性变和(或)钙化。但Xp11.2易位性肾癌镜下见细胞形态有两种,一种呈腺管状、乳头状或实片性生长,胞浆丰富,嗜酸性,异型性明显,可见典型的砂砾体。另一种多呈巢状分布,胞浆稀少,砂砾体少见,而透明细胞癌呈腺泡状排列,胞质透亮,无砂砾体形成。免疫组织化学方面,Xp11.2易位性肾癌特征性表达TFE3核蛋白,肾透明细胞癌高表达CK、CD10、波形蛋白,不表达TFE3核蛋白,本组病例Xp11.2易位性肾癌全部表达TFE3,肾透明细胞癌全部不表达。一些其他的检查方法如细胞核型分析尤其是光谱核型分析需获得新鲜冷冻组织,临床上较少采用。较灵敏的RT-PCR检测也受RNA提取等因素的制约。而荧光原位杂交(FISH)快速、高效的特点已经成为确诊Xp11.2易位性肾癌的金标准。

2 结果

314例肾癌患者均行手术治疗,Xp11.2易位性肾癌患者中12例行根治性肾切除;肾透明细胞癌患者中211例行根治性肾切除,91例行保留肾单位手术。术后随访发生转移者共27例,Xp11.2易位性肾癌患者4例,肺转移2例,骨转移、脑转移各1例,其中儿童和青少年患者(<18岁)均未发现肿瘤转移;肾透明细胞癌患者23例,肺转移14例,骨转移3例,脑转移2例,其他部位转移4例。转移患者部分行舒尼替尼或索拉非尼的靶向药物治疗,其中2例Xp11.2易位性肾癌患者分别于术后12、48个月发生脑、肺转移,服用舒尼替尼治疗,

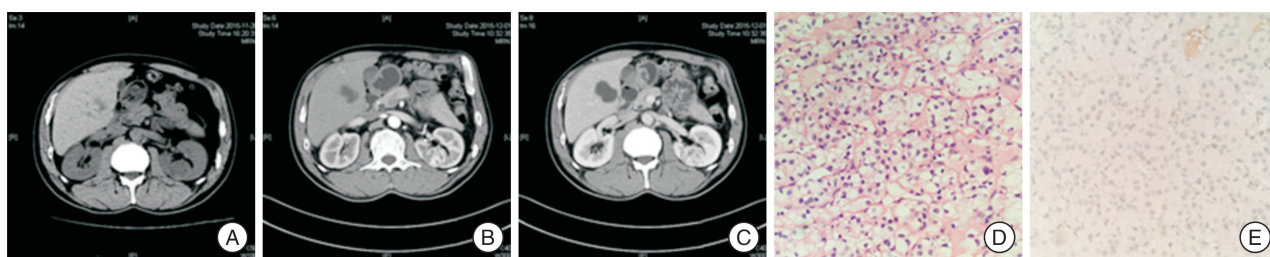
于术后 43、62 个月死亡；3 例肾透明细胞癌患者分别于术后 17、42、63 个月发生肺、脑、骨转移，舒尼

替尼或索拉非尼治疗后于术后 30、50、71 个月死亡。



A:平扫密度稍增高,可见环形钙化;B、C:动脉期缓慢强化,静脉期继续强化,可见坏死、出血;D:Xp11.2 易位性肾癌不含砂砾体(HE×20);E:Xp11.2 易位性肾癌免疫组化显示 TFE3 弥漫性阳性(EnVision 法×20)。

图 1 Xp11.2 易位性肾癌



A:平扫低密度;B:动脉期可见肿瘤内强化明显,高于周围肾实质;C:静脉期可见肿瘤强化程度减低,低于周围肾实质;D:肾透明细胞癌病理图片呈腺泡状排列,胞质透亮(HE×20);E:肾透明细胞癌 TFE3 阴性(EnVision 法×20)。

图 2 肾透明细胞癌

3 讨论

Xp11.2 易位性肾癌以 X 染色体上 TFE3 基因发生断裂易位所形成的融合基因为特征,其易位核型分别有 t(X;1)(P11.2;q21)、t(X;1)(p11.2;p34)、t(X;17)(p11.2;q25)以及 inv(X)(p11;q12)和 t(X;17)(p11.2;q23),产生的融合基因分别有 SPL-TFE3、PRCC-TFE3、PSF-TFE3、NoNo-TFE3 及 CLTC-TFE3^[4]。Xp11.2 易位性肾癌发病年龄较肾透明细胞癌低,且女性高发,可能系女性含有 2 个 X 染色体所致。目前统计的临床资料显示,在所有 Xp11.2 易位性肾癌患者中,45 岁以下人群占 71%,且多数以肉眼血尿就诊,提示该肿瘤具有较高的集合系统侵袭性。肾透明细胞癌男性的发病率明显高于女性,且多数以健康查体就诊,发病年龄较大。CT 方面,Xp11.2 易位性肾癌平扫 CT 值高于肾透明细胞癌,增强扫描肿瘤动脉期中等程度强化(83.4±40.1 HU),静脉期持续强化(95.8±39.1 HU),延迟期缓慢衰减(80.4±30.1 HU),反观肾透明细胞癌,动脉期快速强化(133.4±37.1 HU),静脉期快速衰减(102.8±19.1 HU),延迟期继续衰减(87.4±29.1 HU)。两种肾癌强化特点的不同可能与肿瘤生长模式和血管分布及出血等因素有关。Kim 等^[5]发现肾透明细胞癌的强化程度在所有肾癌类型中是最高的,CT 值可超过

100 HU,与本组资料一致,这或许给临床医师提供了诊断思路,但单纯从 CT 上确诊两种肾癌尚有困难。因 MRI 检查对此两种肾癌的诊断价值有限,影像学以增强 CT 为主要参考依据;病理特点方面,Xp11.2 易位性肾癌的诊断目前主要依靠其特征性表达的 TFE3 核蛋白,本组资料全部表达 TFE3 核蛋白,而肾透明细胞癌全部不表达。Argani 等^[6]报道 TFE3 免疫组化的准确性和特异性分别是 97.5%和 99.6%,但 Klatt 等^[7]报道部分经 FISH 确诊的 Xp11.2 易位性肾癌患者中未见 TFE3 的表达,而且,TFE3 免疫组化也存在一定的假阳性和假阴性可能,比如抗原过度回收、抗体浓度过高、取材不正确等^[7],因此这一数据有待于大样本资料去验证。FISH 可让 Xp11.2 易位性肾癌的诊断更加准确,但由于目前的检测费用问题,并非所有医院都开展,因此 TFE3 免疫组化仍是检测 Xp11.2 易位性肾癌的主要方法。肾透明细胞癌高表达 CK、CD10、波形蛋白,因此联合应用 CD10、波形蛋白、CK 抗体有助于明确肾透明细胞癌的诊断^[8]。在治疗上,因 Xp11.2 易位性肾癌肿瘤体积较大且易发生远处转移,此肾癌首选根治性肾切除^[9],本组资料全部选择根治性肾切除术,虽有报道此类肾癌可行保留肾单位手术^[10],但笔者认为术前结合其临床资料和影像学检查若考虑 Xp11.2

易位性肾癌可能性大时,结合其易侵犯孟盖系统及发生远处转移的特点,多应采取根治性肾切除术。对术后发生远处转移的患者应采用舒尼替尼或索拉非尼为主的靶向药物治疗可适当延长生存期^[11]。但随访发现,Xp11.2 易位性肾癌对靶向治疗虽有疗效,但总体有效率还是小于肾透明细胞癌。本组4例Xp11.2 易位性肾癌的转移患者中,2例在服用舒尼替尼治疗后虽在短时间内有一定疗效,但在35和56个月后转移灶扩大,并于43和62个月死亡。23例肾透明细胞癌转移患者中,3例在服用舒尼替尼或索拉非尼治疗后30、50、71个月死亡。肾透明细胞癌对靶向药物的反应率明显优于Xp11.2 易位性肾癌。目前的文献关于Xp11.2 易位性肾癌的靶向报道较少,疗效也难以判断。但考虑到Xp11.2 易位性肾癌的发病年龄特点和靶向药物的毒性和对生长发育的影响,对于小于18岁的儿童和青少年,慎重行靶向治疗。据文献报道,虽然不同年龄段的Xp11.2 易位性肾癌患者有着相同的组织学形态,但他们的生物学行为却截然不同,因此我们认为Xp11.2 易位性肾癌儿童及青少年患者的预后较成人要好^[12]。本组有3例儿童及青少年患者术后随访72个月,均未发现肿瘤转移。对于肾透明细胞癌,T_{1a}期或T_{1b}期患者可行保留肾单位手术,而T₂期以上建议行根治性肾切除术减少复发,预后较好。

综上所述,Xp11.2 易位性肾癌与肾透明细胞癌在临床、影像学、病理上有一定特点,但还不足以在术前加以鉴别,确诊还要依靠病理,因Xp11.2 易位性肾癌有集合系统侵袭性,如术前可疑此肾癌,建议行根治性肾切除术来提高总体生存率。

[参考文献]

- 1 那彦群,叶章群,孙颖浩,等. 中国泌尿外科疾病诊断治疗指南[M]. 2014版. 北京:人民卫生出版社,2014:1-3.
- 2 Qu Y,Gu C,Wang H,et al. Diagnosis of adults Xp11.2 translocation renal cell carcinoma by immunohistochemistry and FISH assays: clinicopathological data from ethnic Chinese population[J]. *Sci Rep*,2016,6:21677.
- 3 Eble J N,Sauter G,Epstein J I,et al. World Health Organization Classification of tumours. Pathology and genetics of tumors of the urinary system and male genital organs[M]. Lyon:IARC Press,2004:23-42.
- 4 Cheng X,Gan W,Zhang G,et al. Clinical characteristics of XP11.2 translocation/TFE3 gene fusion renal cell carcinoma:a systematic review and meta-analysis of observational studies[J]. *BMC Urol*,2016,16(1):40.
- 5 Kim S H,Kim C S,Kim M J,et al. Differentiation of Clear Cell Renal Cell Carcinoma From Other Subtypes and Fat-Poor Angiomyolipoma by Use of Quantitative Enhancement Measurement During Three-Phase MDCT [J]. *AJR Am J Roentgenol*,2016,206(1):W21-28.
- 6 Argani P,Lal P,Hutchinson B,et al. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions:a sensitive and specific immunohistochemical assay[J]. *Am J Surg Pathol*,2003,27(6):750-761.
- 7 Klatt T,Streubel B,Wrba F,et al. Renal cell carcinoma associated with transcription factor E3 expression and Xp11.2 translocation: incidence, characteristics, and prognosis[J]. *Am J Clin Pathol*,2012,137(5):761-768.
- 8 邹泓,庞丽娟,胡文浩,等. 肾细胞癌的临床病理与免疫表型研究[J]. *中华病理学杂志*,2008,37(11):726-731.
- 9 Klaassen Z,Tatem A,Burnette J O,et al. Adult Xp11 translocation associated renal cell carcinoma: time to recognize[J]. *Urology*,2012,80(5):965-968.
- 10 Suzigan S,Drut R,Faria P,et al. Xp11 translocation carcinoma of the kidney presenting with multilocular cystic renal cell carcinoma-like features[J]. *Int J Surg Pathol*,2007,15(2):199-203.
- 11 Malouf G G,Camparo P,Oudard S,et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma(RCC): a report from the Juvenile RCC Network[J]. *Ann Oncol*,2010,21(9):1834-1838.
- 12 Xu L,Yang R,Gan W,et al. Xp11.2 translocation renal cell carcinomas in young adults[J]. *BMC Urol*,2015,15:57.

(收稿日期:2016-08-15)