Juxtaglomerular cell tumor with pulmonary metastases: A case report and review of the literature

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June 10, 2022

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To the Editor: Juxtaglomerular cell tumor (JGT) is a relatively rare, benign renin-producing tumor that causes hypertension, hyperaldosteronism, and hypokalemia due to excessive renin secretion. Here, we report a case of malignant JGT with pulmonary metastases. A 7-year-old male patient was referred to the hospital for proteinuria found during a school medical checkup. An ultrasound examination revealed a tumor on the right kidney. His blood pressure was 170/120 mmHg, and plasma renin activity was high at 30 ng/mL/hr. Computed tomography (CT) revealed a mass of 3.4 cm diameter on the right kidney with multiple pulmonary metastases, which was suggestive of nephroblastoma. He underwent right nephrectomy, resulting in a return of blood pressure and plasma renin activity to normal levels (reference range, 0.2–2.3 ng/mL/hr). Gross examination of the tumor revealed a 3.2 × 3.2 × 10-cm yellowish-white mass with necrosis in the mid pole of the kidney. Most of the tumor was covered with a fibrous membrane that partially extended into the normal tissue. Histology revealed a mesenchymal neoplasm with a blastemal component that was suggestive of nephroblastoma. No vascular invasion was observed within the analyzed area (Supplemental Figures S1, S2). Subsequently, he received chemotherapy according to the DD-4A regimen of the National Wilms Tumor Study Group. The immunophenotype demonstrated renin and CD34 positivity (Supplemental Figures S3, S4). This led to a definitive diagnosis of JGT, which was consistent with the clinical feature of hypertension. Chemotherapy was stopped at week 6, at which point CT revealed unchanged metastatic lung lesions. He then underwent a two-stage surgical resection for bilateral lung metastases, and total resection was achieved. Pathologically, the metastatic lung lesions were consistent with the resected renal tumor. Because no reports of effective chemotherapy for malignant JGT were found, we followed-up this patient without administering adjuvant chemotherapy. He showed no evidence of disease after a 2-year follow-up. Targeted DNA sequencing using FoundationOne® CDx detected six genetic mutations:*NOTCH3* T272M, *BRAF* D22N, *MAP3K1* L78P, *CDKN2B*A56D, *DAXX* E451del, and *ERBB4* P3L in the primary tumor.

JGT is a rare benign tumor that is more common in relatively young adults. JGT causes various clinical symptoms, such as headache, nausea, dizziness, weakness, hypertension, and proteinuria.[1,2]JGT is generally curable by surgical resection, and tumor removal results in the improvement of hyperreninemia and clinical symptoms.[1] Immunohistochemically, the diagnosis is confirmed by renin positivity in the cytoplasm. In addition, CD34, CD117, vimentin, and ACTA2 are often positive.[2,3]Although JGT is generally considered benign, eight malignant or pathologically atypical cases have been reported in the literature (Table).[3–10] Six were adult cases, and one was a pediatric case. In all cases, the tumor diameter was relatively large (>5 cm). Pathologically, seven of eight showed either vascular invasion or mitotic figures, and among these cases, four had distant metastasis: case 1 demonstrated bilateral lung metastases 6 years after nephrectomy,[4] case 4 demonstrated bilateral lung metastases at initial diagnosis,[9] case 6 demonstrated multicentric synchronous disease in the liver and spleen,[7] case 8 succumbed to hepatic and bone metastases 10 months after nephrectomy.[3] In our case, complete metastasectomy of the bilateral pulmonary nodules was achieved after nephrectomy. Thus, he was in remission at 2 years without adjuvant chemotherapy.

Ours is the first reported case of pediatric malignant JGT with multiple pulmonary metastases. Although most patients with malignant JGT present with a large tumor that is pathologically characterized by vascular invasion, our case had a relatively small-sized tumor with no vascular invasion or nuclear atypia. Few reports have described genetic abnormalities in JGT. Targeted DNA sequences in our case revealed six gene mutations although the significance of these mutations in the pathogenesis of malignant JGT is unclear. A previous study reported that the *NOTCH3* receptor is highly expressed in reninoma in mice.[11] Dysregulation of *NOTCH3* signaling plays a role in soft tissue tumor pathogenesis.[12] Therefore, the *NOTCH3* mutation in our case might have been involved in this malignant transformation. In addition, *NOTCH3* signaling has shown to contributed to chemoresistance to doxorubicin[13], which was consistence with the clinical feature of an ineffective for metastatic lung lesions after chemotherapy including doxorubicin. JGT is generally considered to be a benign tumor, but malignant cases have recently been reported. Our patient was successfully treated with complete pulmonary metastasectomy after primary tumor resection without adjuvant chemotherapy. Pulmonary metastasectomy represents an effective approach in the treatment of JGT-related lung metastases alone. However, no established reports on the prognosis and treatment of malignant JGT exist;

thus, additional case reports are needed.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

1. McVicar M, Carman C, Chandra M, Abbi RJ, Teichberg S, Kahn E. Hypertension secondary to renin-secreting juxtaglomerular cell tumor: case report and review of 38 cases. Pediatr Nephrol 1993;7:404-412.

2. Kuroda N, Gotoda H, Ohe C, et al. Review of juxtaglomerular cell tumor with focus on pathobiological aspect. Diagn Pathol 2011;6:80.

3. Zhou J, Zheng S, Zhang Y, et al. Juxtaglomerular cell tumor: clinicopathologic evaluation in a large series emphasizing its broad histologic spectrum. Pathol Int 2020;70:844-856.

4. Duan X, Bruneval P, Hammadeh R, et al. Metastatic juxtaglomerular cell tumor in a 52-year-old man. Am J Surg Pathol 2004;28:1098-1102.

5. Beaudoin J, Périgny M, Têtu B, Lebel M. A patient with a juxtaglomerular cell tumor with histological vascular invasion. Nat Clin Pract Nephrol 2008;4:458-462.

6. Shera AH, Baba AA, Bakshi IH, Lone IA. Recurrent malignant juxtaglomerular cell tumor: a rare cause of malignant hypertension in a child. J Indian Assoc Pediatr Surg 2011;16:152-154.

7. Cucchiari D, Bertuzzi A, Colombo P, et al. Juxtaglomerular cell tumor: multicentric synchronous disease associated with paraneoplastic syndrome. J Clin Oncol 2013;31:e240-e242.

8. Munakata S, Tomiyama E, Takayama H. Case report of atypical juxtaglomerular cell tumor. Case Rep Pathol 2018;2018:6407360.

9. Huang PW, Lin YC, Wu KF, Sheng TW, Su PJ. Juxtaglomerular cell tumor with lung metastases in a young male patient. *J Cancer Surviv* . 2019;6(3):128.

10. Hagiya A, Zhou M, Hung A, Aron M. Juxtaglomerular cell tumor with atypical pathological features: report of a case and review of literature. Int J Surg Pathol 2020;28:87-91.

11. Martini AG, Xa LK, Lacombe M-J, et al. Transcriptome analysis of human reninomas as an approach to understanding juxtaglomerular cell biology. Hypertension 2017;69:1145-1155.

12. Raimondi L, Ciarapica R, De Salvo M. Inhibition of Notch3 signalling induces rhabdomyosarcoma cell differentiation promoting p38 phosphorylation and p21(Cip1) expression and hampers tumour cell growth in vitro and in vivo. Cell Death Differ 2012;19:871-881.

13. Xiu M, Wang Y, Li B, et al. The Role of Notch3 Signaling in Cancer Stemness and Chemoresistance: Molecular Mechanisms and Targeting Strategies. Front Mol Biosci. 2021;14:694141.

Figure legends

Figure S1. Neoplastic cells with an ovoid shape proliferate in a solid sheet growth pattern, 40×.

Figure S2. Neoplastic cells display rare mitotic activity and mild nuclear atypia, 200×.

Figure S3. Neoplastic cells show CD34 labeling, 200×.

Figure S4. Renin is diffusely distributed in the tumor cytoplasm, 200×.

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