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Case Report

Brain Infarcts: Description of a New Paraneoplastic Phenomenon in the Setting of Wilms Tumor

Srikaran Kalahasti[1], Sim Berlene Mariano[1] and Sathyaprasad Burjonrappa[2]*

[1] *Medical Student, Rutgers Robert Wood Johnson Medical School, Rutgers University, USA.*

[2] *Professor of Surgery, Rutgers Robert Wood Johnson Medical School, Rutgers University, USA.*

***Corresponding Author:** Dr. Sathyaprasad Burjonrappa, MD, MBA, FACS, FRCS (Ed), FSMBS, Professor of Surgery, Medical Education Building Rm 5001 Robert Wood Johnson Place, New Brunswick, NJ 08901, Tel: 732 235 7821, Fax: 732 235 8878, USA.*

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Abstract

We present the case of a 23-month-old male with a one-year history of intermittent abdominal pain who presented for a routine well-child visit and was incidentally noted to have a large abdominal mass and regression of developmental milestones. Upon further investigation, the child was diagnosed with Wilms Tumor (WT) with metastases to the periaortic lymph nodes and bilateral lungs. Initial management included left radical nephrectomy, lymphadenectomy, and mediport placement for chemotherapy infusions. Tumor cytogenetic report was positive for loss of heterozygosity at 11p15 region and pathology demonstrated blastema predominant WT. Treatment decision was based on a therapeutic clinical trial (AREN0534) outlined by the Children's Oncology Group and the patient was placed on a 28-week chemotherapy regimen, including vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide in conjunction with radiation. MRI of the head showed no evidence of metastasis, however it demonstrated multiple areas of infarction in the distribution of the posterior cerebral artery (PCA). Coagulation studies were performed to evaluate possible underlying causes and the patient was found to be heterozygous for Factor V Leiden (FVL) mutation. While FVL is associated with an increased risk of venous thromboembolic (VTE) events, arterial thromboembolic events are generally rare. In this report, we explore potential etiologies for the unique presentation of brain infarction in a pediatric patient with WT.

***Keywords:** Wilms Tumor, brain infarction, coagulopathies, thromboses, paraneoplastic phenomenon, metastases*

Introduction

WT is the most common malignant renal tumor in children accounting for 6% of childhood cancers and over 90% of all pediatric kidney tumors.[1] Abdominal pain is the most common complaint, reported to occur in 30–40% of WT patients, with hypertension, hematuria, and fever seen in 5–30%. WT is also notable for thrombotic manifestations via extension into the renal vein with intravascular thrombi reported in 20–35% of patients.[1] While involvement of the inferior vena cava (IVC) was reported in 4–10% of cases, a thrombus reaching the right atrium was seen in less than 1% of all patients.[2,3] In advanced disease, patients have also been known to present with polycythemia, hemorrhage, or respiratory symptoms secondary to lung metastases.[4] Very rarely, brain metastases and coagulopathies, including acquired Von Willebrand Disease (VWD) and consumption coagulopathies have also been observed.[5-8] Despite these reports, intracranial thromboses have not been noted. We report the case of a 23-month-old boy with WT, who presented with regression of developmental milestones and focal neurological deficits in the setting of intracranial infarction associated with a new diagnosis of WT.

Case Report

Patient was a 23-month-old boy without significant past medical history who was noted by his parents to have intermittent abdominal pain and distension (left greater than right) for the past year and more recently some regression in milestones. At initial evaluation, parents reported the patient was a healthy child with no history of fevers, chills, night sweats, anorexia, weight loss, nausea, vomiting, or other systemic concerns and had displayed usual activity level. They noted on prior routine well-child visits, they had been advised the patient's abdominal symptoms were attributed to reflux, constipation and/or lactose sensitivity and had been managed accordingly. Despite this his abdominal symptoms progressed.

At his routine two-year well-child visit, the pediatrician appreciated an abdominal mass on physical exam and referred him to have abdominal imaging performed. Of note, the patient's father reported a history of stage IV WT, diagnosed at age 2, and underwent a unilateral nephrectomy, suggesting a possible genetic predisposition. Upon further evaluation, the family also stated concerns regarding recent regression in the patient's developmental milestones. Parents noted the patient had previously been able to speak several words but starting several weeks prior to admission was only able to communicate through grunts. Parents also reported sporadic abnormal eye movements. These symptoms had not been observed in prior routine evaluations of the patient.

Ultrasound demonstrated a large left renal mass prompting further imaging and admission to the inpatient service at the hospital. CT of the chest/abdomen/pelvis revealed a 12x12x9 cm mass arising from the left kidney, raising concern for possible WT with adjacent periaortic lymphadenopathy and innumerable bilateral pulmonary lesions, suggestive of metastatic disease (Figure I). He underwent a preoperative Echocardiogram showed no evidence of tumor thrombus. The preoperative laboratory values were normal with a hematocrit of 35. Decision was made to perform a left radical nephrectomy, lymphadenectomy, and placement of a mediport for chemotherapy infusions. Post-operative course was significant for failed initial extubation, likely secondary to metastatic tumor burden on the lungs, and fever of unknown source.

Pathology findings were significant for blastema predominant WT and periaortic lymph nodes positive for metastatic disease. Cytogenetic report revealed no abnormalities; however, oncology microarray analysis was noted to be positive for loss of heterozygosity at the 11p15 region.[9] Additional testing for methylene tetrahydrofolate mutations demonstrated no abnormalities. Following on the pathology findings and in concordance with a therapeutic clinical trial for WT (AREN0534) outlined by the Children's Oncology Group, the patient was initiated on a 28-week chemotherapy regimen incorporating vincristine, dactinomycin doxorubicin, cyclophosphamide, carboplatin, and etoposide in conjunction with radiation.[10] [10] He received 450cGY radiation to bilateral lung fields as well as abdominal flank radiation 1080cGY due to the favorable histology, node positive disease process. The medial border of the radiation field was set 1 cm beyond vertebral body on the contralateral side excluding contralateral kidney; The lateral border was 1 cm away from tumor; and superior/inferior borders again were 1cm away from tumor and included the para-aortic nodes in the radiation field.

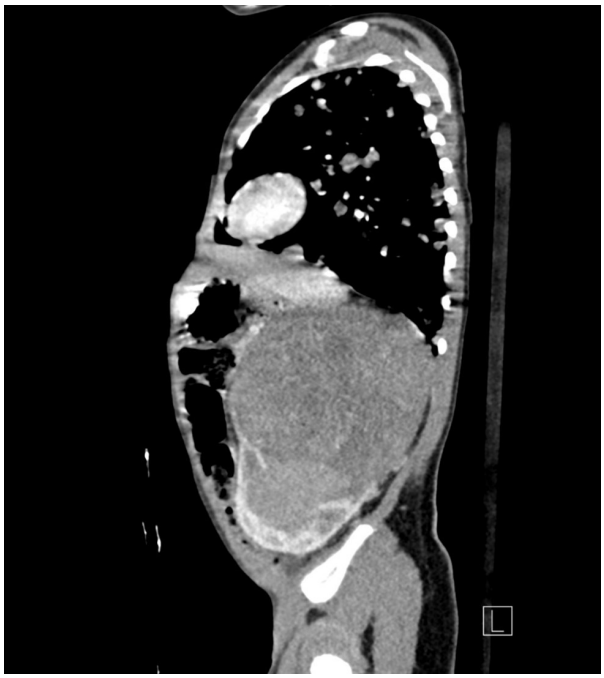

Figure 1: *Large left Wilms tumor with diffuse lung metastasis.*

Post-operative MRI of the brain revealed multiple areas of infarction in the right cerebellar hemisphere, right occipital lobe, right medial temporal lobe, and right posterior parietal lobe (Figures II and III). MRA was performed for evaluation of the posterior cerebral artery distribution and showed no significant abnormalities. Shunting from right to left at the atrial and ventricular level was excluded based on detailed evaluation of cardiac anatomy on echocardiography and bubble studies. Coagulation studies were within normal limits; however, genetic testing noted the patient to be heterozygous for FVL. Due to concerns for cancer-induced hypercoagulable state and thromboembolic events, the patient was placed on enoxaparin and anti-Xa levels were periodically monitored to ensure therapeutic dosing.

After the initial round of chemotherapy, imaging was repeated for re-evaluation of metastatic progression. MRI of the brain revealed no evidence of metastasis and showed the prior infarction as well as cortical atrophy and encephalomalacia. MRA and MRV of the head and neck showed no abnormalities. MRI of the abdomen revealed no residual tumor and no metastasis to the right kidney. Repeat CT of the chest showed improved metastatic burden to the bilateral lungs.

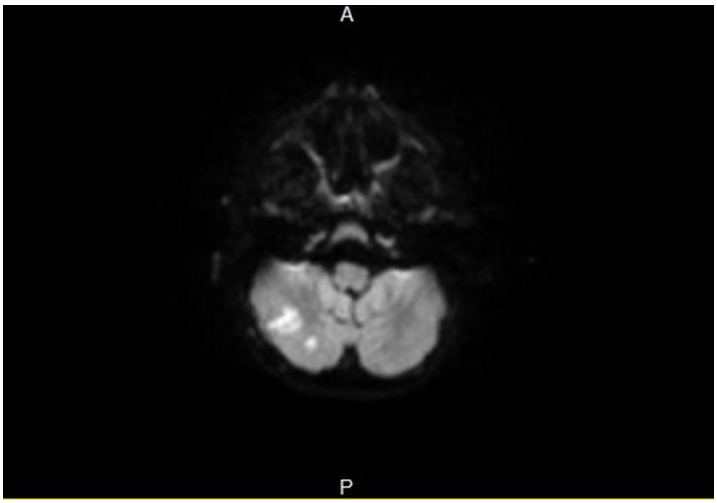

Figure 2: *Infarcts in the Cerebellum on MR Imaging*

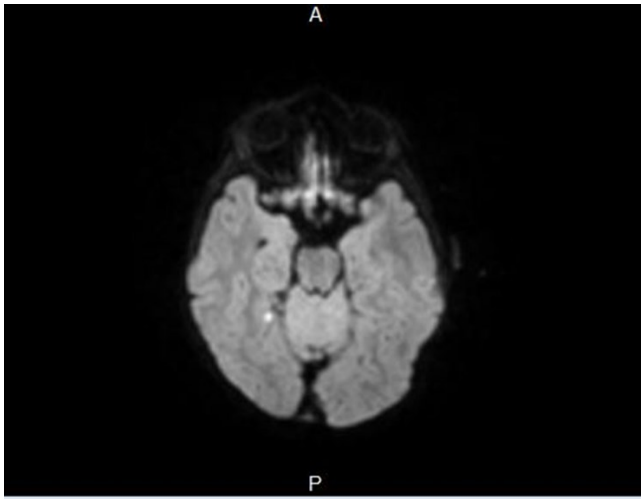

Figure 3: *Infarct in the Right Cerebral Hemisphere*

Over the course of his three-month hospitalization, the patient had gradual improvement of his neurological condition. At the time of discharge, he was noted to be playful and active. Post-discharge, the patient continued routine outpatient chemotherapy and radiation. He also remained on enoxaparin for VTE prophylaxis and amlodipine for management of hypertension secondary to the WT. Six months after initial presentation, the patient was meeting appropriate developmental milestones and continued to have regular follow up with pediatric hematology-oncology. He recently completed his chest radiation and has been scheduled for removal of his mediport after complete resolution of his disease.

Discussion and Conclusion

Brain metastases, coagulopathies, and VTE have been rarely noted in association with WT. In rarer cases, paraneoplastic syndromes have been observed in the setting of malignancies.[11] Various known paraneoplastic manifestations include hypertension, erythrocytosis, hypercalcemia, Cushing syndrome, Lambert-Eaton Myasthenic Syndrome, and acquired Von Willebrand disease.[12,13] Despite these reports, intracranial thromboses have not been reported in cases of WT. To our knowledge, this is the first reported case of a pediatric patient presenting with regression of developmental milestones due to brain infarction in the setting of WT. It is unclear why the thrombotic process just affected the cerebral circulation in this patient. Below we discuss plausible etiologies for the patient's unique presentation.

WT is known to spread to local abdominal lymph nodes, as well as spread via hematogenous metastases to the lungs, and occasionally to the liver. While metastases to the brain are more commonly seen in Small Cell Lung cancer, breast, melanoma, colon, Renal Cell Cancer, and thyroid cancer, WT has rarely been noted to metastasize to the brain.[5,14] Metastatic disease to the brain is thought to involve a complex relationship between the cancer cell's genetic features, the circulatory pathways, and the brain cellular architecture. Extensive radiological imaging, including CT chest/abdomen/pelvis, CTA head, MRI head, and MRA/MRV head conducted during the patient's hospital course demonstrated metastatic spread to the periaortic lymph nodes and lungs bilaterally but demonstrated no evidence of metastases to the brain.

Non-bacterial thrombotic endocarditis (NBTE) is a known cause of ischemic stroke in certain solid tumor malignancies, notably pancreatic adenocarcinoma.[15] While extension of WT into the right atrium via the IVC has been noted, cases of associated NBTE have not been observed. Additionally, evaluation for congenital or acquired cardiac anatomical abnormalities warranted echocardiography due to concerns for possible paradoxical embolus to the brain. However, the studies showed no evidence of a patent foramen ovale or right to left shunting in this patient and did not demonstrate marantic vegetations, decreasing the likelihood of ischemic stroke secondary to cardiac emboli. Another concern was potential air embolism during the mediport placement. MRI findings excluded air embolism based on location as well as infarct patterns. (Venous air embolism usually involves the frontal sulci and has a serpiginous pattern. Arterial air embolism usually is due to a significant injection of air across the venous system (>2ml/Kg) that overwhelms pulmonary resorptive capacity or due to shunting between the right and left sided circulation. The latter appear as punctate air densities with surrounding infarction). The MRI findings in this patient did not suggest air embolism and the Mediport placement itself was uncomplicated.

There are several potential mechanisms by which vasculitides, a group of autoimmune diseases, may be associated with an increased risk of malignancy.[16, 17] However, the temporal association between vasculitides and malignancy has not been adequately explained.[18] While vasculitides that increase the risk of stroke may present in some malignancies, as seen in patients with polyarteritis nodosa in the setting of hairy cell leukemia, it remains a rare occurrence in WT.[19, 20] In this patient, MRA of the head and neck and rheumatological studies were unremarkable, making brain injury secondary to vasculitis less likely.

In some instances of WT, acquired VWD has been noted, likely secondary to a paraneoplastic process.[21] Coagulation studies performed during the patient's hospital course showed no abnormalities associated with VWD-related coagulopathy. However, the patient was noted to be heterozygous for FVL, a condition known to be independently associated with an increased risk of VTE as well as marginally increased risk of ischemic stroke, relative to noncarriers.[22, 23] In the setting of cancers, FVL has also been noted to further increase the risk of cancer-associated thrombosis.[24] In this patient, a paraneoplastic phenomenon secondary to WT in the context of FVL, a prothrombotic risk factor, may suggest a possible synergistic relationship between the two disease processes, creating a predisposition for arterial thromboembolic events. While we treated this infant with a prothrombotic condition and thrombosis in the brain with long term anticoagulation after surgical resection of the malignancy, we would recommend multidisciplinary management of children presenting with this clinical picture and consider anticoagulation on a case by case basis.

With the development of treatment regimens, the current cure rate for WT is greater than 85% .[25] It is important to consider possible pathologic processes in the setting of WT which may complicate the clinical presentation and subsequent management. Such is the case in this WT patient presenting with brain infarctions in the distribution of the PCA. Etiologies including metastasis, NBTE, paradoxical emboli, vasculitis, and acquired VWD were investigated and found to be unlikely given the countervailing evidence. In light of this unique presentation of WT and considering the potential synergistic interactions between the hypercoagulable state associated with cancer, underlying genetic risk factors, and the potential for paraneoplastic phenomena in malignancies, we recommend close neurological follow-up to monitor changes in developmental milestones, especially in younger patients at risk for WT.

References

1. Al Diab A, Hirmas N, Almousa A, et al. Inferior vena cava involvement in children with wilms tumor. *Pediatr Surg Int.* 2017;33(5):569-573. doi: 10.1007/s00383-016-4034-7.

2. Giannoulia-Karadana A, Moschovi M, Koutsovitis P, Tolis G, Tzortzatou-Stathopoulou F. Inferior vena cava and right atrial thrombosis in children with nephroblastoma: Diagnostic and therapeutic problems. *J Pediatr Surg.* 2000;35 (10):1459-1461. doi: 10.1053/jpsu.2000.16414.

3. Zeng J, Zheng J, Yu H. A child with tumour thrombus extending to the right atrium. E*ur Heart J.* 2015;36(27):1713. doi: 10.1093/eurheartj/ehu429.

4. Leung RS, Liesner R, Brock P. Coagulopathy as a presenting feature of wilms tumour. *Eur J Pediatr.* 2004;163(7):369-373. doi: 10.1007/s00431-004-1443-8.

5. Akakin A, Yilaz B, Eksi MS, Yapcier O, Kilic T. Relapsed wilms' tumor with multiple brain metastasis. *Korean journal of pediatrics;* 2016; 59:S96-S98. Doi:10.3345/kjp.2016.59.11.S96.

6. Peterson NE, Galloway B. Wilms tumor with consumption coagulopathy. *Urology.* 1982;19(1):74-77. doi: 10.1016/0090-4295(82)90053-X.

7. Wang AH, Gibbons ISE, Nedwich A, Barbero GJ. Wilms' tumor associated with venous thrombosis and consumption coagulopathy. *Am J Dis Child.* 1972;123(6):599-601. doi: 10.1001/archpedi.1972.02110120123019.

8. Singh S, Singh D, Baheti G, Karmarkar SJ. Coagulopathy associated with wilms' tumour: A rare complication. *Ped Surgery Int.* 2003;19(4):296-297. doi: 10.1007/s00383-002-0853-9.

9. Grundy P, Telzerow P, Moksness J, Breslow N. Clinicopathologic correlates of loss of heterozygosity in Wilms' tumor: A preliminary analysis. *Medical and pediatric oncology.* 1996;27(5):429-433. doi:10.1002/(SICI)1096-911X(199611) 27:5<429::AID-MPO7>3.0.CO;2-O

10. Ehrlich P, Chi YY, Chintagumpala MM, et al. Results of the first prospective multi-institutional treatment study in children with bilateral wilms tumor (AREN0534): A report from the children's oncology group. *Ann Surg.* 2017 Sep;266 (3):470-478. doi: 10.1097/SLA.0000000000002356.

11. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment [published correction appears in Mayo Clin Proc. 2011 Apr;86(4):364. Dosage error in article text]. *Mayo Clin Proc*. 2010;85(9):838-854. doi:10.4065/mcp.2010.0099

12. Coppes MJ. Serum biological markers and paraneoplastic syndromes in Wilms tumor. *Medical and Pediatric Oncology*. 1993;21(3):213-221. doi:10.1002/mpo.2950210311.

13. Petersen CL, Hemker BG, Jacobson RD, Warwick AB, Jaradeh SS, Kelly ME. Wilms tumor presenting with Lambert-Eaton myasthenic syndrome. *J Pediatr Hematol Oncol*. 2013;35(4):267-270. doi:10.1097/MPH.0b013e31828d46a7

14. Riihimäki M, Thomsen H, Sundquist K, Sundquist J, Hemminki K. Clinical landscape of cancer metastases. *Cancer Med.* 2018;7(11):5534-5542. doi:10.1002/cam4.1697

15. Harris AZ, Ternouth I, Lallu BD. Case report: marantic endocarditis in renal cell carcinoma: nephrectomy a treatment. *European heart journal : case reports.* 2021;5(11). doi:10.1093/ehjcr/ytab437

16. Kermani TA, Warrington KJ, Amin S. Malignancy risk in vasculitis. *Ther Adv Musculoskelet Dis.* 2011;3(1):55-63. doi:10.1177/1759720X10387460

17. Weyand CM, Goronzy JJ, Kurtin PJ. Lymphoma in rheumatoid arthritis: an immune system set up for failure. *Arthritis Rheum.* 2006;54(3):685-689. doi:10.1002/art.21674

18. Hutson TE, Hoffman GS. Temporal concurrence of vasculitis and cancer: A report of 12 cases. *ARTHRIT CARE RES.* 2000;13(6):417-423. doi: 10.1002/1529-0131(200012)13:6<417::AID-ART13>3.0.CO;2-T.

19. Hasler P, Kistler H, Gerber H. Vasculitides in hairy cell leukemia. *Semin Arthritis Rheum.* 1995;25(2):134-142. doi:10.1016/s0049-0172(95)80026-3

20. Fain O, Hamidou M, et al. Vasculitides associated with malignancies: Analysis of sixty patients. *Arthritis & Rheumatism.* 2007;57(8):1473-1480. doi:10.1002/art.23085. 21.

21. Chiasakul T, De Jesus E, Tong J, et al. Inherited Thrombophilia and the Risk of Arterial Ischemic Stroke: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2019;8(19):e012877. doi:10.1161/JAHA.119.012877

22. Hirmerova J, Seidlerova J, Subrt I. The association of factor V Leiden with various clinical patterns of venous thromboembolism--the factor V Leiden paradox. *QJM: An International Journal of Medicine.* 2014;107(9):715-720. doi:10.1093/qjmed/hcu055.

23. Hamedani AG, Cole JW, Mitchell BD, Kittner SJ. Meta-analysis of factor V Leiden and ischemic stroke in young adults: the importance of case ascertainment. *Stroke*. 2010;41(8):1599-1603. doi:10.1161/STROKEAHA.110.581256

24. Pabinger I, Ay C, Dunkler D, et al. Factor V Leiden mutation increases the risk for venous thromboembolism in cancer patients - results from the Vienna Cancer And Thrombosis Study (CATS). *J Thromb Haemost.* 2015;13(1):17-22. doi:10.1111/jth.12778

25. Aldrink JH, Heaton TE, Dasgupta R, et al. Update on Wilms tumor. *J Pediatr Surg*. 2019;54(3):390-397. doi:10.1016/j.jpedsurg.2018.09.005

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