Wilms Tumor with Pleural Metastasis

Global Pediatric Health
Volume 7: 1–5

DOI: 10.1177/2333794X20952292
journals.sagepub.com/home/gph
SAGE

Ameer Al-Hadidi, MD[1], Morta Lapkus, MD[1], Nathan M. Novotny, MD, FACS, FAAP[1,2], L. Kate Gowans, MD[3], Peter Y. Chen, MD[4], and Anthony Stallion, MD, FACS, FAAP[1,2]

Received February 28, 2020. Received revised July 19, 2020. Accepted for publication July 31, 2020.

Introduction

Wilms tumor is the most common primary renal tumor, second most common intraabdominal tumor, and fourth most common overall malignancy in children with a peak incidence between ages 2 and 3.[1-4] Metastatic disease is seen in a minority of patients and most commonly located in the lung parenchyma. However, metastatic disease to the pleura with subsequent presentation of a pleural effusion is exceedingly rare and seldomly described. We discuss an interesting case along with a review of the available literature on the incidence, management, and long-term outcomes for malignant pleural effusions in the setting of Wilms tumor.

Ethical Approval and Informed Consent

According to the Beaumont Research Institute policy, neither approval from the ethics committee nor informed consent from the study population was required given the number of cases being presented.

Case Presentation

A 12-year-old female with a past medical history of sickle cell trait presented to the emergency department (ED) with 2 days of right-sided abdominal pain, nausea, vomiting, fevers, and fatigue. Her abdomen was soft, non-distended, with right-sided tenderness and a palpable mass. Computed tomography (CT) of the abdomen/pelvis with oral and intravenous contrast demonstrated a large, heterogeneous mass in the right kidney measuring 12.8 × 9 cm with subcapsular and perinephric hemorrhage (Figure 1). The left kidney was unremarkable. Chest CT was unremarkable for metastatic disease or pleural effusion. She underwent a right radical nephrectomy with lymph node sampling. The tumor had intraoperatively ruptured posteriorly and at the superior pole. The hilar, para-caval, and para-aortic regions were evaluated and only 1 hilar lymph node was found. Pathology was consistent with stage-III ruptured Wilms tumor with favorable histology, without loss of heterozygosity (LOH) for chromosomes 1p and 16q, negative final margins, and invasion through the renal capsule into perinephric soft tissue without extension into adjacent organs or the main renal vein. There was lymphovascular involvement in the renal sinus. The hilar lymph node was negative for metastatic disease. Pathology was confirmed by expert consultation at the Children's Oncology Group (COG) Renal Tumor Pathology Center.

After multidisciplinary discussion, our patient was treated according to the COG guidelines for standard risk patients (defined as stage-III, favorable histology, without LOH 1p and 16q) and completed 1 week of radiation therapy directed at the tumor bed, as rupture was very limited and localized to the flank, and 6 months of chemotherapy consisting of vincristine, actinomycin D, and doxorubicin. One year after completing therapy, she presented with abdominal pain, distension, constipation, and fatigue. CT and MRI of the abdomen/pelvis revealed a large, vascular, heterogeneous mass with solid and cystic components consistent with intraperitoneal tumor with areas of necrosis and associated hemorrhagic ascites that filled the pelvis causing a mass effect. The tumor involved the root of the mesentery with evidence of multiple omental and peritoneal masses from the diaphragm to the pelvis. Ultrasound-guided biopsy was

[1]Department of General Surgery, Beaumont Health, Royal Oak, MI, USA
[2]Department of Pediatric Surgery, Beaumont Children's, Beaumont Health, Royal Oak, MI, USA
[3]Department of Hematology-Oncology, Beaumont Children's, Beaumont Health, Royal Oak, MI, USA
[4]Department of Radiation Oncology, Beaumont Health, Royal Oak, MI, USA

Corresponding Author:
Anthony Stallion, MD, FACS, FAAP, Department of General Surgery, Beaumont Health, 3535 W. 13 Mile Rd Ste 307, Royal Oak, MI 48073, USA.
Email: Anthony.Stallion@beaumont.org

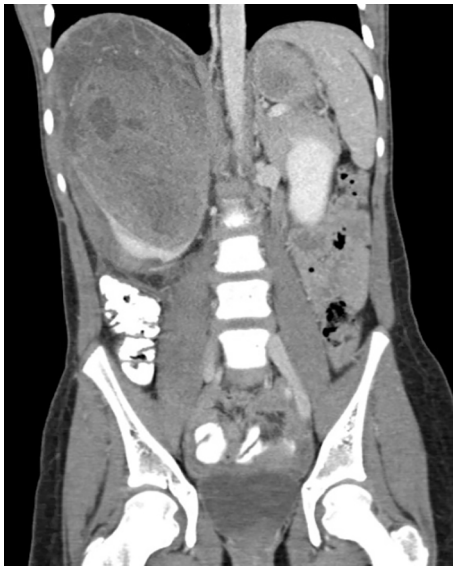

Figure 1. Computed tomography of the abdomen/pelvis with oral and intravenous contrast demonstrating mass in the right kidney.

consistent with recurrence of Wilms tumor with favorable histology. Chest imaging was unremarkable for metastatic disease; however, it did demonstrate bilateral pleural effusions with atelectasis without any signs of mediastinal adenopathy. Given the extensive disease and tumor encasement of multiple large vessels, salvage chemotherapy with 6 cycles of ICE (ifosfamide, carboplatin, and etoposide) was initiated prior to surgical debulking. Following the second cycle, repeat MRI demonstrated extensive decrease in tumor bulk with no evidence of ascites or pleural effusions. She underwent an exploratory laparotomy for excision of residual tumor and subsequently underwent radiation therapy to the pelvis.

Four months after completing therapy, follow-up imaging revealed a trace right-sided pleural effusion with slightly increased pleural thickening along the posterior aspect of the right middle lobe and a new 3.6 × 3.6 × 3.8 cm soft tissue density adjacent to the dome of the liver concerning for tumor recurrence. Ultrasound-guided biopsy confirmed recurrent Wilms tumor.

Before chemotherapy was resumed, she developed progressively worsening shortness of breath and presented to the emergency department with tachypnea. Chest imaging demonstrated a massive right pleural effusion with mass effect on the heart, mediastinal shift, and associated complete atelectasis of right lung. (Figure 2A and B) Additionally, there was interval development of a 11.6 × 6.5 × 5.8 cm pleural mass at the inferior aspect of the right hemi-thorax. The previously noted mass at the dome of the liver had progressed in size. No pleural effusion was appreciated on the left side. A thoracentesis was performed with removal of >1500 cc of serosanguineous fluid. Cytology of the pleural fluid comprised tumor cells similar in morphology to the previously resected specimen and immunohistochemistry and immunofluorescence were consistent with Wilms tumor, indicating a malignant effusion.

The effusion resolved with chest tube drainage and initiation of salvage chemotherapy with vincristine, irinotecan, and temozolamide, and whole-lung and abdomen radiation therapy with a boost to the pleura and hepatic dome of the diaphragm.

Follow-up CT revealed near complete resolution of previous pleural thickening and nodularity. Five months later, follow-up imaging demonstrated recurrent tumor within the abdomen and pelvis associated with ascites, but no evidence of a pleural effusion. She was restarted on chemotherapy with vincristine, irinotecan, and temozolomide. She was not felt to be a candidate for radiation.

Discussion

Wilms tumor is the most common primary renal tumor, second most common intraabdominal tumor, and fourth most common overall malignancy in children with a peak incidence between ages 2 and 3.[1-4] A critical prognostic factor that profoundly impacts outcomes is histology. Ninety percent of patients present with favorable histology, which is associated with >90% survival.[5] Older age at diagnosis (>4 years old) and tumor rupture with spillage are considered negative prognostic factors associated with higher risks of relapse and mortality.[6-9] Metastatic disease at presentation is seen in 12% of patients with 80% of lesions located within the pulmonary parenchyma.[10,11] However, the presence, subsequent management, and prognosis of pleural metastasis is very rarely described.

A retrospective analysis of patients with Wilms tumor at St. Jude Children's Research Hospital over a 16-year period identified only 10 out of 233 patients (4.3%) with a pleural effusion on pre-nephrectomy CT imaging.[10] All occurred on the side of the tumor, none had tumor invasion of the diaphragm, and 6 had concurrent ascites (3 with pre-nephrectomy tumor rupture). Only 2 patients underwent a thoracentesis, both without any evidence of malignant cells. All 10 patients had complete resolution of their pleural effusions following treatment for local staging with no mortality or recurrence at 68 months of median follow-up. Two of the 10 patients did receive pulmonary irradiation for stage IV disease.[10] The etiology of pleural effusions are numerous. While undergoing

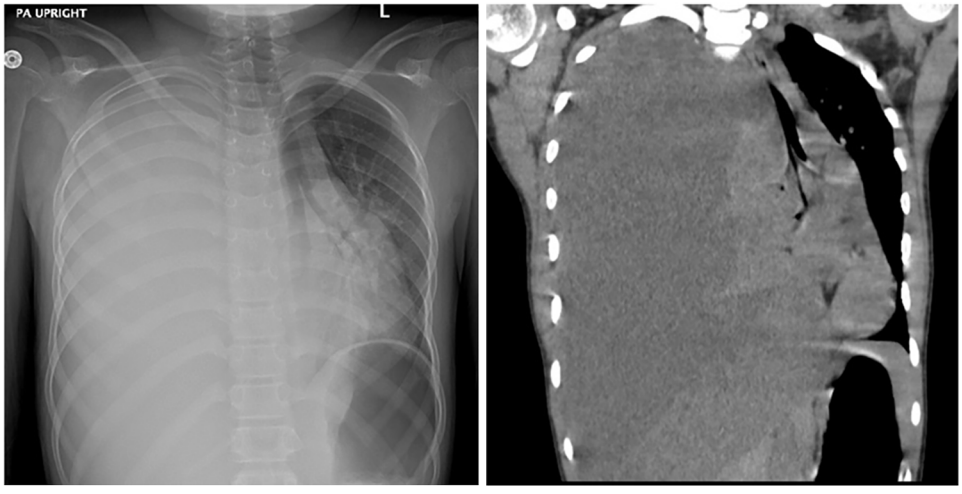

Figure 2A and B. Chest imaging demonstrated a massive right pleural effusion with mass effect.

cytotoxic chemotherapy and radiation, infection and drug-induced liver dysfunction (leading to hypoalbuminemia and subsequent development of anasarca, ascites, and pleural effusions) are potential causes.[12] Resolution of pleural effusions may be secondary to resolution of the initial insult or, if truly malignant, adequate treatment with chemotherapy. However, since the majority of the effusions were not investigated for malignant cells, no definitive conclusions can be drawn.

There are only a few reported cases of confirmed malignant effusions in the setting of Wilms tumor. An autopsy study identified pleural metastasis in 10 of 43 patients with Wilms tumor; however, clinical presentation and symptoms of these patients are unknown.[13] Consequently, there is no consensus on the treatment of malignant effusions. One report describes a patient with a confirmed malignant effusion who, due to the size of the primary tumor and concern for disseminated disease, underwent neoadjuvant chemotherapy. There was considerable reduction in tumor size and complete resolution of the pleural effusion. Upon parental request to avoid possibly unnecessary radiation, the patient underwent close follow-up in place of pulmonary irradiation and after 8-years remained disease-free.[14] Two other cases were identified where patients improved after receiving chest irradiation.[12,15] One was a patient who presented clinically unstable with a large intraabdominal tumor and, shortly after starting abdominal radiation, developed a symptomatic pleural effusion requiring a thoracentesis which revealed the diagnosis of Wilms tumor. Abdominal radiation therapy was extended to the affected hemi-thorax with the addition of vincristine and actinomycin D. The patient had a good response with no recurrence after 4.5 years.[15]

At least 60% of young adults who are survivors of a childhood cancer suffer from a chronic health problem.[5] With excellent outcomes following treatment of Wilms tumor, efforts to reduce toxicity of therapy due to significant long-term sequelae from treatment are emerging. This can be accomplished by reducing intensity, duration, and number of therapeutic agents. Furthermore, there is growing evidence supporting the avoidance of unnecessary radiation therapy to the chest in patients with a rapid response to initial chemotherapy in the setting of pulmonary parenchymal metastasis.[16] Radiation has been shown to cause restricted spinal growth, scoliosis, secondary malignancies (sarcomas, breast cancer, lymphoma/leukemia, melanoma, GI tumors) where approximately 70% occur within the radiation field, and may present issues with fertility and childbirth (spontaneous miscarriage, restricted fetal growth, premature or low-birth weight birth, and early menopause).[5,17-19] Furthermore, pulmonary irradiation can be associated with diffuse interstitial pneumonitis, restrictive lung disease, cardiomyopathy (particularly if doxorubicin is used as a radiation sensitizer), and female breast cancer (cumulative incidence of 30% by age 50).[11,20-22]

In the setting of cytological confirmation of a malignant effusion, withholding pulmonary radiation therapy would be exceedingly controversial given the lack of data supporting outcomes of limited therapy.[10,14] When our patient presented with recurrent abdominal disease, asymptomatic bilateral pleural effusions were identified on CT imaging along with tumor deposition on the

diaphragm. Similar to the previously mentioned case, the pleural effusions resolved after systemic chemotherapy and abdominal radiation for her local disease. However, 4 months after completion of her therapy, routine follow-up imaging identified a mass at the dome of the liver and pleural thickening with a trace right-sided pleural effusion that significantly progressed and became symptomatic within a matter of a few weeks and required chest tube drainage. After cytology findings were consistent with a malignant effusion, the patient underwent whole lung radiation with a boost to the pleura and hepatic dome. Follow-up imaging revealed complete resolution of the pleural effusion and near complete resolution of the pleural disease. No subsequent pleural effusions were identified on imaging within the 13-months following radiation therapy. Notably however, she was restarted on chemotherapy within that period for recurrent intraabdominal disease.

Conclusion

Given the low occurrence of pleural effusions associated with Wilms tumor, and the remarkably rare instances of confirmed malignant effusions, the ideal management of pleural effusions in the setting of Wilms tumor is unknown. Further investigation is required to identify potential risk factors (like pleural thickening or diaphragmatic involvement) for malignant etiology of pleural effusions and to identify the most appropriate and least toxic method of treatment.

Author Contributions

AA and ML drafted the manuscript. NV, KG, PC, and AS critically revised the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Ameer Al-Hadidi https://orcid.org/0000-0002-2416-6449

References

1. Ries LAG, Smith MA, Gurney JG, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. *NIH Pub No 99-4649*; 1999.
2. Feuer EJ., Cronin KA. (eds) *National Cancer Institute: SEER Cancer Statistics Review 1975-2012*. National Cancer Institute; 2015.
3. St. Jude Children's Research Hospital. Wilms tumor. https://www.stjude.org/disease/wilms-tumor.html
4. *Childhood and Adolescent Cancer*. American Cancer Society, Inc. 2018.
5. Wright KD, Green DM, Daw NC. Late effects of treatment for Wilms tumor. *Pediatr Hematol Oncol*. 2009;26:407-413. doi:10.1080/08880010903019344
6. Pritchard-Jones K, Kelsey A, Vujanic G, Imeson J, Hutton C, Mitchell C. Older age is an adverse prognostic factor in stage I, favorable histology Wilms' tumor treated with vincristine monochemotherapy: a study by the United Kingdom Children's Cancer Study Group, Wilm's Tumor Working Group. *J Clin Oncol*. 2003;21:3269-3275. doi:10.1200/JCO.2003.01.062
7. Irtan S, Jitlal M, Bate J, et al. Risk factors for local recurrence in Wilms tumour and the potential influence of biopsy - the United Kingdom experience. *Eur J Cancer*. 2015;51:225-232. doi:10.1016/j.ejca.2014.10.026
8. Brisse HJ, Schleiermacher G, Sarnacki S, et al. Preoperative Wilms tumor rupture: a retrospective study of 57 patients. *Cancer*. 2008;113:202-213. doi:10.1002/cncr.23535
9. Shamberger RC, Guthrie KA, Ritchey ML, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. *Ann Surg*. 1999;229:292-297. doi:10.1097/00000658-199902000-00019
10. Corey B, Yang C-H, Wilimas JA, Davidoff A, Dome JS. Significance of pleural effusion at diagnosis of Wilms tumor. *Pediatr Blood Cancer*. 2004;42:145-148. doi:10.1002/pbc.10429
11. Green DM, Breslow NE, Evans I, Moksness J, D'Angio GJ. Treatment of children with stage IV favorable histology Wilms tumor: a report from the National Wilms Tumor Study Group. *Med Pediatr Oncol*. 1996;26:147-152. doi:10.1002/(SICI)1096-911X(199603)26:3<147::AID-MPO1>3.0.CO;2-K
12. Betkerur U, Lanzkowsky P. Pleural effusion in Wilms' tumor. *J Pediatr Surgery1*. 1977;12:523-525.
13. Bannayan GA, Huvos AG, D'Angio GJ. Effect of irradiation on the maturation of Wilms' tumor. *Cancer*. 1971;27:812-818. doi:10.1002/1097-0142(197104)27:4<812::AID-CNCR2820270409>3.0.CO;2-E
14. Canpolat C, Jaffe N. Wilms' tumor: cure of malignant pleural effusion exclusively with chemotherapy. *Med Pediatr Oncol*. 1995;24:274-277. doi:10.1002/mpo.2950240413
15. Jaffe N, Jockin H, Tefft ME, Traggis D, Filler R. Wilms tumor: diagnosis by thoracentesis. *Chest*. 1973;64:130-132.
16. Dix DB, Seibel NL, Chi YY, et al. Treatment of stage IV favorable histology wilms tumor with lung metastases: a report from the children's oncology group AREN0533 study. *J Clin Oncol*. 2018;36:1564-1570. doi:10.1200/JCO.2017.77.1931

17. Breslow NE, Takashima JR, Whitton JA, Moksness J, D'Angio GJ, Green DM. Second malignant neoplasms following treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol*. 1995;13:1851-1859. doi:10.1200/JCO.1995.13.8.1851
18. Wallace WHB, Shalet SM, Morris-Jones PH, Swindell R, Gattamaneni HR. Effect of abdominal irradiation on growth in boys treated for a wilms' tumor. *Med Pediatr Oncol*. 1990;18:441-446. doi:10.1002/mpo.2950180602
19. Mäkipernaa A, Heikkilä JT, Merikanto J, Marttinen E, Siimes MA. Spinal deformity induced by radiotherapy for solid tumours in childhood: a long-term follow up study. *Eur J Pediatr*. 1993;152:197-200. doi:10.1007/BF01956143
20. Green DM, Finklestein JZ, Tefft ME, Norkool P. Diffuse interstitial pneumonitis after pulmonary irradiation for metastatic Wilms' tumor. A report from the National Wilms' tumor study. *Cancer*. 1989;63:450-453. doi:10.1002/1097-0142(19890201)63:3<450::AID-CNCR2820630310>3.0.CO;2-T
21. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol*. 2001;19:1926-1934. doi:10.1200/JCO.2001.19.7.1926
22. Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol*. 2014;32:2217-2223. doi:10.1200/JCO.2013.54.4601