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Research

Is there an Association between Pulmonary Metastases and Wilms Tumour Histopathology?

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ABSTRACT

Aim: To evaluate if Wilms tumour histopathology predicts occurrence of pulmonary metastases and the response of lung metastases to preoperative chemotherapy.

Methods: Seventy-nine patients under age 16 years were identified with Wilms tumour in 1988–2015. All thoracic CT-images before and after preoperative chemotherapy with suspected metastases were re-evaluated. Tumour volumes were measured from CT- or MRI-images (available in 52/79 patients). Tumour samples from both pre-treatment cutting needle biopsies (CNB) and from nephrectomy were re-evaluated (59/79).

Results: Pulmonary metastases were found in 14 out of 79 (18%) patients. Patients with pulmonary metastases had larger Wilms tumour volume (903 ml (IQR 807-1215) vs. 428 ml (IQR 299-765), p<0.001), and tended to have predominance of blastemal cells in diagnostic CNB (75% (IQR 50-97) vs. 50% (IQR 20-80), p=0.064) compared to those without pulmonary metastases. At nephrectomy samples, the proportion of necrosis was higher in patients with metastases (95% (IQR 76-99) vs. 60%, (IQR 20-96), p=0.026). In six cases (43%), the pulmonary metastases disappeared with preoperative treatment. Disappearance of metastases was not associated with original renal tumour volume or tumour shrinking or final tumour histology. However, blastemal cell content at diagnosis was larger in the cases with persisting metastases (85% (IQR 73-94) vs. 50% (IQR 30-50), p=0.027).

Conclusion: Pulmonary metastases are more common in children with a large Wilms tumour especially when the proportion of blastemal cells is high. Half of the pulmonary metastases disappeared during the preoperative chemotherapy. Large blastemal cell content at diagnosis was associated with persisting metastases.

Keywords: Wilms tumour, Histology, Metastasis, Preoperative chemotherapy, Tumour volume.

INTRODUCTION

The prognosis of Wilms tumour patients is excellent with three year overall survival (OS) of 89% [1]. However, the survival has been better (96%) in patients without metastases than in patients with metastases (75%). Accordingly, more intense chemotherapy with anthracyclins and local radiotherapy are needed to improve the prognosis of patients with metastases [1-4]. Recently even 95.6% 4-year survival rates have been achieved in tumours with favourable histology, despite the presence of metastases [5].

Approximately 10-14% of the patients with Wilms tumour have been reported to have pulmonary metastases at diagnosis [1,4]. In previous reports, pulmonary metastases have been associated with larger Wilms tumour volume and with a higher local stage (2 and 3) of tumour. The response of the metastases to preoperative chemotherapy is shown to be of prognostic importance [3]. However, to our knowledge, there are no published studies evaluating the association between primary tumour histology and response of pulmonary metastases to preoperative chemotherapy. In this study, we evaluated the association between tumour histology in diagnostic Core Needle Biopsy (CNB) and occurrence of pulmonary metastases in chest-CT. In addition, we studied if the tumour histology before or after preoperative chemotherapy was associated with the response of pulmonary metastases to preoperative chemotherapy.

METHODS

The study cohort was identified by a retrospective review of the surgical database for patients operated for renal tumours in 1988 through 2015 at the Children´s Hospital, University of Helsinki. The study was reviewed and approved by the Institutional Ethics Committee.

Patients and pulmonary metastases

Altogether 90 patients with renal tumours were found of whom 79 had Wilms tumour. Fourteen patients (18%) with Wilms tumour were diagnosed to have pulmonary metastases in the initial thoracic CT-scan. The thoracic CT-scans were re-evaluated by radiologist (OL). Lung nodules were considered as metastatic

disease if they were round, noncalcified, and not in a pulmonary fissure [5]. The metastases were classified as proposed by Cohen [6]. According this non-validated classification, the patient is considered to have low metastatic tumour burden if he/she had up to five nodules less than 1 cm in diameter or up to two nodules less than 2 cm in diameter. Intermediate tumour burden classified as patient having 6-20 nodules less than 1 cm, or 3-10 nodules less than 2 cm or any nodule 2-5 cm in diameter and high tumour burden if any nodule was more than 5 cm in diameter or more than 11 nodules less than 2 cm in diameter or more than 20 metastatic nodules irrespective of size. Original CT- or MRI-images of the tumours were available for 52 patients and were also re-evaluated by radiologist for the exact renal tumour volume with ellipsoid formula (0.523 × a × b × c) [1].

Tumour histology

Seventy of 79 Wilms tumour patients had undergone CNB at diagnosis. The 59 Wilms tumour patients who had both diagnostic CNB samples and histological samples from nephrectomy available for re-evaluation were included in the final analysis. The pathology slides were re-evaluated by pathologist (JL) and clinician (MT) to confirm the diagnosis and to evaluate the proportions of cellular components of Wilms tumour (epithelial, blastemal, and stromal) in CNB samples. In addition, the response to preoperative chemotherapy was classified according to the current guidelines. The structured histological evaluation included the estimation of the degree of necrosis (necrotic=100% necrosis, regressive=66-99% necrosis, poor response=necrosis<66%), proportions of cellular components of Wilms tumour (epithelial, blastemal, stromal) expressed as a percent of the total surface area of the viable tumour tissue, and presence of anaplasia (focal or diffuse) [7,8]. The chemotherapy regimen used preoperatively was based on dactinomycin and vincristine intensified with alkylators or anthracycline in patients with metastases [9].

Statistical analysis

Continuous variables (patient age, tumour volume and proportion of cellular elements in histological samples) are expressed as medians and interquartile ranges (IQR) or ranges and they were compared with Mann-Whitney test. Categorical variables were compared with Fisher's exact test. For the analyses Statview® 5.0.1, SAS Institute Inc., was used, p-value<0.05 was considered significant.

RESULTS

Tumour histology and metastases

Fourteen out of the 59 study patients had lung metastases and they were older than those without metastases (p=0.043) **(Table 1).** In re-evaluation, high, intermediate or low metastatic burden was found in five, two and seven patients, respectively. The patients with metastases had significantly (p<0.001) larger primary tumour volume, but the change in the primary tumour volume during preoperative therapy was similar in the patients with and without metastases **(Table 1).** In addition, the tumour samples at diagnosis tended to have higher proportion of blastemal cells in patients with metastases compared to those without metastases (p=0.064) but not after the preoperative therapy. However, the proportion of stromal and epithelial cells was similar in cases with and without metastases. In nephrectomy samples, the proportion of necrosis was higher in patients who had metastases at diagnosis compared to those without metastases (p=0.026). Pulmonary metastases were found in 1/6 patients with low risk, in 12/47 patients with intermediate risk and in in 1/6 patients with high risk tumours.

Response to chemotherapy

According to original medical records, pulmonary metastases disappeared in 11 out of 14 (79%) patients during the preoperative chemotherapy. However, in re-evaluation, a complete response in pulmonary metastases was confirmed only in six (43%)

Table 1. Characteristics of Wilms tumours in patients with and without pulmonary metastases.

	No metastases (n=45)	Metastases (n=14)	p Value
Age at diagnosis (years)	2.8 years (IQR 1.7-4.4)	4.1 (IQR 3.0-5.6)	0.043
tumor volume at DG (ml)	430 (IQR 301-784)	927 (IQR 842-1112)	<0.001
Tumors volume at operation (ml)	162 (IQR 61-344)	196 (IQR 127-400)	0.273
Change in tumor volume (%)	-60 (-83-36)	-78 (IQR -86-61)	0.258
Histological composition at DG			
Blastemal cells (%)	50 (IQR 20-80)	73 (IQR 50-88)	0.064
Stromal cells (%)	30 (IQR 8-70)	23 (IQR 10-50)	0.408
Epithelial cells (%)	5 (IQR 0-10)	2 (IQR 0-5)	0.407
Histological composition in nephrectomy specimen			
Degree of necrosis (%)	60 (IQR 20-95)	95 (IQR 80-99)	0.026
Blastemal cells (%)	5 (IQR 0-61)	43 (IQR 0-70)	0.531
Stromal cells (%)	19 (IQR 0-60)	10 (IQR 0-30)	0.515
Epithelial cells (%)	15 (0-42)	20 (IQR 0-45)	0.836
Histological classification (nephrectomy)			
Necrotic	5	1	0.167
Regressive	16	10	0.014
Mixed	8	2	0.702
Blastemal	4	0	0.312
Stromal	8	0	0.086
Epithelial	3	0	0.548
Diffuse anaplasia	1	1	>0.99
Local stage			
Stage 1	30	7	0.363
Stage 2	6	3	
Stage 3	9	4	

cases (5/7 with low metastatic tumour burden and in 1/5 with high metastatic tumour burden, but in neither of the two with intermediate metastatic burden, (p=0.103 for low metastatic burden vs. the others). In patients with persisting metastases high or intermediate metastatic tumour burden decreased to low burden after preoperative chemotherapy. Disappearance of metastases was not associated with original renal tumour volume or tumour shrinking or final tumour histology. However, blastemal cell content at diagnosis was larger in the cases with persisting metastases (85% (IQR 73-94) vs. 50% (IQR 30-50), p=0.027).

Outcome of the patients

During the interval of follow-up (median) of 10.6 years (IQR 5.1-14.5, range 0.5-24.7), two of 59 patients (3%) have deceased. Both had pulmonary metastases at diagnosis. Their metastases disappeared during the preoperative chemotherapy, but later the metastases recurred leading to death 0.5 and 1.1 years postoperatively. The other had mixed (blastemal and stromal) histology and the other had pure blastemal histology at pre-treatment CNB. In the nephrectomy specimen, other had diffuse anaplasia and the other had regressive type histology respectively. In all other patients, the metastases disappeared at latest during the adjuvant therapy. In addition, two patients with no pulmonary metastases at diagnosis developed metastases during the first year after nephrectomy. However, their metastases disappeared later with adjuvant therapy and these patients have now survived 3.8 and 13.7 years without recurrence. The other had blastemal and the other had mixed type histology in nephrectomy specimen. Both underwent operation for metastases, showing blastemal rich histology.

DISCUSSION

Pulmonary metastases were detected in diagnostic CT-scans in 18% of our Wilms tumour patients. The patients with pulmonary metastases were older, had larger renal tumours and the blastemal cell content in tumour biopsies at diagnosis tended to be more abundant compared to those without metastases. The degree of tumour necrosis in nephrectomy samples was higher in patients with pulmonary metastases. However, the proportion of different Wilms tumour cellular components in nephrectomy samples and the degree shrinkage of the tumours with preoperative chemotherapy were comparable between patients with or without metastases. During the preoperative therapy, 43% of the pulmonary metastases disappeared completely in 50% of the cases the metastases shrank or their amount decreased and the remainder metastases remained essentially unchanged. No difference was observed in the histology of nephrectomy samples between the patients with persisting metastases and in those whose metastases disappeared.

In our study, we used the CT based non-validated classification for pulmonary metastases proposed by Cohen because as far as we know there are no generally accepted classification system [6,10]. However, the clinical impact of the size or amount of metastases remained inconclusive. The use of CT probably explains the higher 18% incidence rate of metastases at diagnosis compared to metastases rate of 10%-13% based on chest X-ray imaging [1,4,11,12]. CT has high sensitivity to detect even small (<1 cm) lesions, but has questionable specificity particularly for the smallest nodules [10,12-14]. Pulmonary nodules can be observed with chest CT in 33-38% of children without malignant disease. Non-metastatic nodules are mainly smaller than 5 mm, predominately located in lower lobes of the lungs and are mostly angular or triangular in shape [15,16]. With modern imaging-technology, non-neoplastic nodules can be more easily differentiated from metastatic nodules than previously. The significance of so-called CT-only nodules in Wilms tumour patients has been controversial. According to recent studies, CT-only nodules may add prognostic information and influence the treatment in some patients [1,12]. In the SIOP 2001 study, survival was worse in the patients with CT-only metastases than in the patients without metastases, but better than in the patients with large metastases [1].

In this study, the patients with metastases were older and their Wilms tumours were larger than in the patients without metastases. This is in line with the previous SIOP/GPOH study [4]. In that study the change in volume of the Wilms tumour during the preoperative therapy was more remarkable in patients with pulmonary metastases compared to others (82.7% vs. 63.3%). We observed a similar, but not significant tendency in our cohort. One explanation is that the patients with metastases got three-drug chemotherapy instead of two-drug treatment. In our study 43% of the pulmonary metastases disappeared completely during the preoperative chemotherapy, which is also in line with previous SIOP 2001 and SIOP/GPOH studies in which 30-61% of the metastases disappeared [1,17]. We observed that the smaller metastases tended to disappear more often during the preoperative chemotherapy, but the significance of this for prognosis remained unclear. The remainder of the pulmonary metastases disappeared during the adjuvant chemotherapy. However, in two patients the metastases reoccurred later leading to death. Two additional patients, who had no metastases at diagnosis, got metastases later, but in those cases, the treatment of metastases has been successful.

Our study has some limitations. The patients were retrospectively collected from a long time and the protocols have changed over the years. In addition, pathology specimens in some patients without pulmonary metastases were not available for re-evaluation. The diagnosis of pulmonary metastases was based on chest CT-s and accordingly the proportion of patients with metastases was greater than in most series relying on chest X-rays. This may influence the comparisons to other studies. However, accurate diagnosis can be considered strength of the study. One limitation is that pre-treatment CNB is not necessarily representative since Wilms tumours are usually heterogeneous. However, multiple CNB's were sampled to avoid sampling error. Other strength of our study is a thorough re-evaluation of both the biopsy specimens, and the lung CT scans and primary tumour CT/MRI images by the same pathologist and radiologist, respectively.

CONCLUSION

We conclude that the patients with pulmonary metastases were older and they had larger tumours than those without. During the preoperative therapy, complete response was observed in 43% of the metastases. Large blastemal cell content at diagnosis was associated with persisting metastases. However, the primary response of metastases or tumour histology (except diffuse anaplasia) was not of prognostic significance.

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