Congenital mesoblastic nephroma fifty years after its recognition: A narrative review

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Congenital mesoblastic nephroma fifty years after its recognition: A narrative review

Running head: Review on congenital mesoblastic nephroma

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Abbreviations key

CMN	Congenital mesoblastic nephroma
BWS	Beckwith-Wiedemann syndrome
AV	Actinomycin and vincristine

Abstract

Congenital mesoblastic nephroma (CMN) is a rare pediatric renal tumor with low malignant potential that most commonly occurs early in infancy. Treatment strategies are based on the few published CMN series, while a significant number of CMN patients have been described in case reports. The aim of this narrative review was to create an up-to-date overview of the literature. Complete surgical removal is curative in most cases. The risk of treatment-related mortality (both surgery- and chemotherapy-related) is relatively high in the first weeks of life, indicating that these young patients deserve special attention with respect to timing and type of treatment.

Introduction

Congenital mesoblastic nephroma (CMN) is a rare tumor with low malignant potential, which represents approximately 3% of all pediatric renal tumors [1-3]. It is the most common renal neoplasm diagnosed in the first month of life [4,5]. CMN is frequently recognized before or at time of birth, illustrating the embryonal character of the disease.

Bolande was the first to use the term 'congenital mesoblastic nephroma' in 1967, though decades earlier this tumor was already described using different terminologies including fetal renal hamartoma and leiomyomatous renal hamartoma [3,6-9]. The histological classification of CMN includes three subtypes, i.e. the classic, cellular and mixed type [10-12]. Recurrent genetic aberrations described in CMN include somatic trisomy 11 and t(12;15)(p13;q25), resulting in a fusion of *ETV6* and *NTRK3* [13,14].

The vast majority of CMN patients seems to present with local disease. Complete nephrectomy is considered the standard of care for children with CMN, although use of adjuvant chemotherapy and even radiotherapy has been reported [2,15,16]. These treatment strategies are mainly based on the few published CMN series with substantial numbers. A significant number of CMN patients have been described in case reports and to date a comprehensive review is not available. The aim of this narrative review was to gain insight into the clinical characteristics, histological subtypes, genetic aberrations, treatment modalities and outcome of patients with CMN, in order to develop future treatment strategies.

Methods

For this review, databases of PubMed, Embase, Web of Science, Scopus and Google scholar were searched using search terms "mesoblastic nephroma", "mesoblast" within 3 words of "nephrom", "non-Wilms" or "not-Wilms" (mesoblastic nephroma*[tw] OR (mesoblast*[tw] NEAR/3 nephrom*[tw])) OR non-Wilms*[tw] OR not-Wilms*[tw]). After removal of double articles, 984 articles published before 1 December 2015 remained (Fig 1). Thirteen articles were added after hand searching. Articles were selected on the basis of title and abstract by two independent reviewers (S.L.G. and T.D.) (Fig 1). To be eligible for inclusion, a study had to (1) contain well-described CMN patients <18 years of age, (2) be an original article, (3) be reported after the study by Bolande et al (1967), (4) be written in English language and (5) be available in full-text. In case of doubt about the histological diagnosis or in case the tumor was described

under a different name, the paper was reviewed extensively by an expert pathologist (G.J.V.) before inclusion in the current review.

Results

A total of 200 articles met the inclusion criteria (Fig. 1). Of these, 25 articles reported series of ≥10 patients which included 628 patients in total (Table 1, Supplemental Table S1). Where more than one paper reported on the same or overlapping cohorts, the report with the most detailed information on the largest number of individuals was used; eventually 12 non-overlapping series including 306 patients were selected for the analysis in this review (Table 1).

In addition to these series, 174 case reports described 270 cases in total (Supplemental Table S2). Data of these case reports were only included in the analysis of this review if they provided well documented data and relevant additional information, such as the correlation between genotype and histology and characteristics of stage III or relapsed CMN patients.

Clinical characteristics

Median age at diagnosis ranged from 0 days (newborn) - 2.3 months (median age ≤1 month in 63% of series) and overall age ranged from prenatal - 3.8 years (Table 1). Prenatal detection of the tumor was reported in 16% of the patients [15,17-19]. The male to female ratio was 1.5:1 (Table 1). The most commonly reported presenting symptom was an abdominal mass, described in 76% of the cases (Table 1). Other repeatedly reported symptoms were hypertension (19%) and hematuria (11%) (Table 1). Case reports additionally reported polyhydramnios in 40/270 cases (15%), hypercalcemia in 12/270 cases (4%) and hyperreninemia in 3/270 cases (1%) (Supplemental Table S2). Both hypercalcemia and hyperreninemia completely resolved with removal of the tumor in all cases [5,20-34].

Congenital anomalies were reported in 11 patients described in series; genitourinary anomalies were described in 6 patients, gastrointestinal malformations in 2 patients, polydactyly in 1 patient, hydrocephalus in 1 patient and 1 patient was described to be diagnosed with the Beckwith-Wiedemann syndrome (BWS) [2,15,18,35]. In case reports, 2 additional patients with BWS were diagnosed with CMN [5,36].

Pathology

CMN is classified into three histological subtypes: classic, cellular and mixed type. Classical type CMN shows a leiomyomatous pattern resembling infantile fibromatosis composed of interlacing bundles of spindle cells and low mitotic activity, no capsule, infiltrative growth into the renal parenchyma and/or perirenal fat, and entrapped islands of parenchyma [37]. The cellular type, identical to infantile fibrosarcoma, shows dense cellularity, a strong hemangiopericytous vascular pattern and a high mitotic activity but less infiltrative growth into the renal parenchyma [10,37]. Mixed type CMN shows a mixture of these two patterns in any proportion [37]. Information on histological subtype was available for 231 patients; the classic type occurred in 91 patients (39%), the cellular type in 96 patients (42%), the mixed type in 23 patients (10%) and classic/mixed type (no discrimination) in 21 patients (9%) (Table 1). In three series a significant difference in age between classic (median age ranging between 6-17 days) and cellular type CMN (median age ranging between 3.7-5 months) was reported [15,16,19]. The median age of mixed type CMN was described in only one series, i.e. 1.9 months [16].

Information on stage was available for 251 patients; stage I/II disease was found in 208 patients (83%) and stage III disease in 42 patients (17%) (Table 1). Reasons for stage III disease were positive surgical margins (n=13), tumor rupture (n=12) or a combination of positive surgical margins and tumor rupture (n=11), while in 8 patients the reason for stage III was unknown [2,10,15-18,38-40]. One patient was described to have stage IV disease because of 'suspected' malignant cells in the bone marrow, however these cells were not histologically proven to be CMN cells, so we consider this case not being stage IV [35]. In case reports, another case was described to have stage IV disease at diagnosis (lesions in the right tibia on CT scan, however no histological confirmation available) [41]. Bilateral (stage V) disease has never been reported. Stage in relation to histological type is presented in Figure 2.

Data on immunohistochemistry were described in one series, showing immunoreactive renin (intense staining in vessels within areas of the trapped cortex) in 10/12 studied cases [38,39]. Case reports provided information on immunohistochemical staining in 53 cases. In these cases, in total 27 different immunohistochemical markers were used. No marker specific for CMN could be identified (Supplemental Table S3).

Genetics

The most commonly reported genetic aberrations in CMN are t(12;15)(p13;q25), leading to a fusion of the genes *ETV6* and *NTRK3*, and trisomy 11 (both somatic). In Table 2, information on stage, histological type and outcome is provided for cases harboring t(12;15)(p13;q25) and cases harboring trisomy 11. In series, t(12;15)(p13;q25) and trisomy 11 were identified in 29% and 54% of the analyzed cases, respectively [13,18,19,40]. No clear relation between stage and genetic subtype could be identified. Both genetic aberrations occurred in mixed/cellular type CMN only, and never in the classic type of CMN (Table 2). Median ages of patients harboring t(12;15)(p13;q25) and patients harboring trisomy 11 were both 1 month.

Other recurrently reported genetic aberrations in CMN (in case reports) are trisomies 8 (n=9), 17 (n=4), 20 (n=4), 7 (n=3), 10 (n=3), 18 (n=2), 2 (n=2) and 9 (n=2) (Supplemental Table S2); all identified aberrations only occurred in mixed/cellular type CMN.

Treatment

Treatment details were available for 263 patients. Pre-operative chemotherapy was administered in only 9 patients, consisting of actinomycin and vincristine (AV) in 8 patients and unknown type of treatment in one patient [15,16,18]. Information on response to pre-operative chemotherapy was described in 6 cases; 5 cases treated with AV showed a reduction in tumor size of at least 30% and one case treated with AV had a significant increase in tumor size, but histology at time of surgery showed 80% necrosis [15,16].

All patients underwent surgery (179 complete nephrectomy, 6 partial nephrectomy (re-excision n=3), 77 unknown type of surgery), except for one patient who died before surgery could be applied.

Post-operative chemotherapy had been administered in 50 patients, consisting of AV in 21 cases, actinomycin alone in 11 cases, AV and doxorubicin in 3 cases, AV and cyclophosphamide in 1 case, etoposide/cyclophosphamide/doxorubicin/carboplatin in one case and in 13 cases type of post-operative chemotherapy was unknown [2,10,15,16,18,35,38,39,42]. Radiotherapy was applied in nine cases [2,10,15,35].

Outcome

Information on outcome was available for 276 patients described in series (Table 1). Of these, 264 patients survived (96%) and 12 patients died (4%). Causes of death in these 12 patients were

disease-related in 5 cases and treatment-related in 7 cases (5 surgery-related, 2 chemotherapy-related) (Supplemental Table S4). Median age at diagnosis of patients who died of disease was 6 months, while median age at diagnosis of patients who died of treatment-related causes was 0 days (newborn). Surgery-related causes of death included post-operative sepsis (n=2), post-operative necrotizing enterocolitis (n=1), intra-operative bleeding (n=1) and 'not specified' (n=1). Chemotherapy-related causes of death consisted of severe neutropenia and sepsis (n=2).

Information on occurrence of relapse was available for all 306 patients described in series. Relapses occurred in 12 patients (4%) (9 local, 2 metastatic in lung and bone, 1 location unknown) (Supplemental Table S5). The histological subtype was known in 11 relapsed cases (8 cellular, 1 classic, 2 mixed). Information on outcome after relapse was available in 10 cases; 6 achieved a second complete remission and 4 patients died of disease (Supplemental Table S5).

Prognostic value of stage, histologic subtype and genetic aberrations

Information on outcome according to stage was available for 145 patients described in series. Of 125 patients with stage I/II disease, 4 patients (3%) suffered from a relapse and 6 patients (5%) died (3 of treatment-related toxicity and 3 of disease) (Supplemental Table S4 and S5). Of note, only 1 of 100 (1%) stage I/II patients treated with surgery alone, developed a relapse. Of 34 patients with stage III disease, 6 patients (18%) had a relapse (4 cellular, 1 mixed, 1 unknown histology) and 2 patients (11%) died of tumor progression (both cellular) (Supplemental Table S4 and S5). As this is only a small set of patients, we also analyzed stage III patients as described in case reports. Stage III patients reported in case reports (n=22), together with stage III patients reported in series (n=34) are described in Supplemental Table S6; 15/56 stage III patients (23%) suffered from a relapse (73% cellular subtype) and 4/56 patients (6%) died of disease (all cellular subtype).

Information on outcome according to histological subtype was available for 156 patients described in series. Of 74 patients with classic type CMN, 1 patient (1%) (stage II) had a relapse and another patient (1%) (stage II) died of surgical complications (Supplemental Table S4 and S5). Of 59 patients with cellular type CMN, 6 patients (10%) (1 stage I, 1 stage II, 4 stage III) had a relapse and 4 patients (7%) (1 stage I, 1 stage II and 2 stage III) died of disease (Supplemental Table S4 and S5). Of 23 patients with mixed type CMN, one patient (4%) (stage III) had a relapse, but was alive after treatment (Supplemental Table S5 and S6).

Outcomes of patients harboring t(12;15)(p13;q25) and trisomy 11 are described in Table 2.

Discussion

The aim of this narrative review was to present a comprehensive and up-to-date overview of clinical characteristics, optimal treatment strategies and outcome of different histological and genetic subtypes of CMN, thereby serving future treatment guideline development for this rare tumor.

Most studies reporting on CMN have not been based on (inter-)national registries. Therefore, the prevalence of CMN and its histological subtypes is hard to analyze. Large series have suggested that CMN comprises 3.5-4% of all pediatric renal tumors, but it is conceivable that perinatal diagnosed cases may have been considered benign, and therefore not have been included in renal tumor registries [15,16]. The frequency of the cellular subtype and classic subtype seems to be similar, while the mixed subtype occurs remarkably less often (±10%) [15,16,19].

CMN most commonly occurs early in infancy and over 15% of the cases are detected prenatally [13,15,16,35,38,39]. Although CMN has been reported in 26 adult patients in literature, it remains uncertain whether these cases are real CMN's [43-62]. It is believed that most of these so-called adult mesoblastic nephromas are now recognized to have represented other tumors, such as metanephric stromal tumor, cystic hamartoma of the renal pelvis or mixed epithelial and stromal tumor [63,64]. For this reason, adult cases have been excluded from the current review.

Two major genetic variants have recurrently been described in CMN; t(12;15)(q13;q25), resulting in a fusion of *ETV6* and *NTRK3*, and trisomy 11 [13,18,19,40]. These genetic aberrations were only identified in cellular and (less common) mixed type CMN. Of interest, the other recurrently but rarely reported genetic aberrations (i.e. trisomy 2/8/9/10/17/18/20) also only occurred in mixed and cellular type CMN [30,65-72]. This clonality may be illustrative for more malignant disease as these are the subtypes that seem to behave more aggressively. However, no biological studies have been performed to functionally verify this, as yet. We assume that all aforementioned genetic aberrations are somatic, since no germline genetic aberrations associated with CMN have been described. This is in line with the observation that bilateral CMN has never been reported. Besides the diagnosis of Beckwith-Wiedemann syndrome in 3 CMN patients, no association with genetic predisposition syndromes has been reported up until now [5,18,36]. Occurrence of CMN in two siblings has been reported once [73].

Overall survival of CMN patients was excellent (5-year overall survival ±95%). Nevertheless, it was not 100% as suggested in earlier reports [16,42]. It is remarkable that causes of death were treatment-related in about half of the cases and most of these patients were very young (median age at diagnosis: 0 days, newborn) [2,10,13,15,17,18,35,38,39]. This underscores that these infants with renal tumors deserve special attention with respect to timing and type of treatment, and need a dedicated expert pediatric oncology setting. Relapses were described in only 4% of the patients [2,13,15,18,19,35]. Virtually all relapses occurred within 12 months after diagnosis, indicating that close monitoring of all cases should be advised for at least 1 year following end of treatment. Most relapses occurred locally, however also metastatic relapses have been reported (Supplemental Table S5). About 69% of the relapsed patients survived after relapse treatment consisting of individualized combinations of surgery, chemotherapy and radiotherapy (Supplemental Table S5) [2,13,15,18,19,35].

Factors that seem to negatively influence outcome of CMN patients were stage III disease and cellular subtype (Supplemental Table S4, S5 and S6) [15]. In addition to these factors, Furtwangler et al. described age ≥ 3 months to be associated with the occurrence of relapse based on a univariate analysis of 50 CMN cases, which can probably be attributed to the observation that the more aggressive cellular subtype occurs most often in older patients [15]. According to the current review, patients with relapse indeed seemed to be slightly older (median age approximately 3.8 months) compared to patients without relapse (median age <1 month) (Supplemental Table S5). In contrast, most deceased CMN patients were relatively young (median age 0 days, newborn), mainly due to the high incidence of treatment-related mortality among these very young patients (Supplemental Table S4). It is currently not possible to elucidate the prognostic value of t(12;15)(p13;q25) and trisomy 11 in CMN patients due to lack of published data [13,18,19].

Designing a standard of care for CMN patients is a challenge based on the limited available evidence. It is obvious that patients with stage I/II disease, representing over 80% of the CMN patients, benefit from a surgery only strategy [15,16,74]. Particularly in CMN cases, removing perirenal fat during surgery is considered the golden standard, as CMN tumors often show infiltrative growth into the perirenal fat [1]. Throughout the world immediate surgery is recommended for renal tumors in patients under 6 months of age due to the higher probability of pathology other than Wilms' tumor in this age group [4,75]. However, consideration of pre-

operative chemotherapy (AV) may be justified in a small subset of these young patients, when imaging or clinical symptoms suggest a high risk of operative or anesthetic complications or inoperability, even by an experienced surgical team. Partial nephrectomy or nephron-sparing surgery has only been performed in a small subset of patients and in 3 of 6 such cases, re-excision was necessary [15]. It is important that, especially in the neonatal setting, the risk of surgery should be weighed carefully against the risk of pre-operative chemotherapy.

Stage III CMN patients represent a challenging subgroup with respect to the development of proper guidelines. For most of the cases surgery only seems to be sufficient, especially for stage III cases of the classic or mixed histological subtype. Of 12 well-documented classic and mixed type stage III patients treated without additional chemotherapy, one patient (8%) suffered from a relapse, but survived after relapse treatment (Supplemental Table S6). In contrast, 7/12 (58%) stage III cases of the cellular type treated with surgery only suffered from a relapse, while 4/14 (29%) stage III cellular type cases treated with adjuvant chemotherapy developed a relapse. Hence, evidence that additional chemotherapy is reasonable for stage III cellular type cases is not available due to a small dataset including selected subjects (Supplemental Table S6) [15,16,18]. Chemosensitivity is documented in CMN patients; treatment of patients with pre-operative actinomycin/vincristine resulted in a reduction in tumor size or necrotizing of the tumor in all reported patients [15,16]. In addition, Loeb *et al* described three patients with recurrent cellular CMN who showed a complete response to different combinations of chemotherapy (Supplemental Table S5) [76]. However, based on the results of this review, caution with respect to chemotherapy-related toxicity is important in these young children (Supplemental Table S4). Targeted therapy might be an option for cases with progressive disease that do not respond to chemotherapy. In particular Crizotinib, an ALK inhibitor which proved to be of benefit for acute lymphoblastic leukemia patients harboring the ETV6-NTRK3 transcript, resulting from the same t(12;15)(p13;q25) as described in CMN cases, could be considered as a potential compound in highly selected aggressive cases [77]. The role of radiotherapy for CMN patients is uncertain, and considering the fact that late effects of radiotherapy are suspected to be substantial in this relatively young group of patients, radiotherapy should be reserved for highly selected, aggressive and chemotherapy resistant cases only.

Because of the small number of relapsed CMN patients and the different treatment regimens applied in these patients, designing evidence-based treatment guidelines for relapsed CMN is not

possible. Treatment of such patients requires an individualized approach in dedicated centers for pediatric oncology.

Based on this overview, we conclude that CMN is a disease that presents at young age, most commonly in the first months of life. Most CMN patients present with stage I/II disease, for which surgery only is the recommended treatment. Based on the very limited available data, partial nephrectomy or nephron-sparing surgery is currently not recommended for CMN patients. There is insufficient evidence for recommending adjuvant chemotherapy in patients with stage III disease, due to the small number of reported cases and lack of clinical trials. Histologically confirmed stage IV or stage V CMN cases have not been described. Although initial surgery is recommended for renal tumors in patients under 6 months of age, consideration of pre-operative chemotherapy may be justified in a small subset of young patients, when imaging or clinical symptoms suggest a high risk of operative of anesthetic complications. Survival rates of reported CMN patients were excellent (approximately 95% overall survival). Factors that seemed to be associated with occurrence of relapse were stage III disease and cellular histology. The prognostic value of t(12;15)(p13;q25) and trisomy 11, only described in cellular and mixed type CMN, is hard to elucidate based on the small number of series with available data. Despite the excellent outcome of patients diagnosed with CMN, the risk of treatment-related complications (both surgery and chemotherapy related complications) seems to be relatively high, especially when the tumor appears in the first weeks of life. This indicates that these very young patients deserve special attention with respect to the timing and type of treatment, that they need a dedicated expert pediatric oncology setting, and that close monitoring of toxicity is needed. It is recommended to discuss rare challenging individual CMN cases (such as (cellular) stage III and relapsed cases) with steering committees of pediatric renal tumor boards, such as SIOP (International Society of Pediatric Oncology) and COG (Children's Oncology Group). The results of this review have guided the design of new CMN treatment recommendations, which will be included in the international SIOP RTSG 2016 UMBRELLA protocol, however they illustrate that longitudinal prospective registries that include histology as well as molecular diagnostics are necessary for further evidence-based treatment and guideline development for patients with CMN.

Conflict of interest statement

The authors declare no conflict of interest.

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Legends

Figure 1: Selection of articles

Figure 2: Stage according to histological subtype (reported in non-overlapping series ≥ 10 cases)

Table 1: Non-overlapping series reporting ≥ 10 CMN patients

Table 2: Stage, histology and outcome of reported CMN cases harboring t(12;15)(p13;q22) or trisomy 11

Supplemental Table 1: Available series reporting ≥ 10 CMN patients

Supplemental Table S2: CMN patients described in case reports

Supplemental Table S3: Immunohistochemical staining of 53 CMN patients described in case reports

Supplemental Table S4: Characteristics and treatment of reported deceased CMN patients

Supplemental Table S5: Characteristics, treatment and outcome of reported relapsed CMN patients

Supplemental Table S6: Characteristics, treatment and outcome of reported stage III CMN patients

Table 1. Non-overlapping series reporting ≥ 10 CMN patients

Author, year	M/F	L/R	Median age (range)	Presenting symptoms				Stage			Treatment				Histologic patterns			Genetics		EFS	OS	Median follow-up (range)
				AM	HT	HE	Other	I/II	III	IV	Pr-CT	S	P-CT	RT	Cl	M	Ce	t(12;15)	Trisomy 11			
1. Howell, 1982	33/18	26/25	2.3m	48	2	9	6	39	12	0	-	51	28	4	NA			NA	NA	98%	98%	3.2y (4m-11.5y)
2. Sandstedt, 1985	11/18	13/16	NA	18	-	5	5	21	8	0	-	29	5	1	9	-	20	NA	NA	93%	93%	> 4y
3. Cook, 1988 / Malone, 1989 ¶	9/3	3/9	3d (1d-2.5y)	11	4	1	NA*	11	1	0	-	12	1	-	NA			NA	NA	83%	83%	7.3y †
4. Barrantes, 1991	8/5	9/4	0d (0d-19m)	NA*	-	-	-	12	0	1 #	-	13	4	3	9	1	3	NA	NA	85%	85%	5.8y
5. Leclair, 2005	NA	NA	NA	NA				25	1	0	-	26	-	-	21		5	NA	NA	96%	96%	±3.5y
6. Anderson, 2006	NA	NA	2m (0d-11m)	NA				11	2	0	-	13	-	-	3	6	4	3/13	NA	85%	100%	NA
7. Furtwaengler, 2006	34/16	21/29	18.5d (0d-2.6y)	27	16	1	6	41	9	0	5	50	6	1	29	-	21	NA	NA	94%	95%	4.2y (0.8-8.3y)
8. Watanabe, 2007	7/6	NA	30d (5d-7m)	NA				NA			NA				4	1	8	8/12	7/13	92%	92%	NA
9. Bayindir, 2009	7/3	5/5	3.1m (6d-5.5m)	9	7	2	4	7	3	0	2	9	2	-	2	2	6	2/10	NA	70%	90%	3.6y (6m-7y) †
10. Chaudry, 2009	15/15	14/16	NA	NA*	-	-	-	NA			NA	30	NA	NA	12	3	15	6/30	NA	93%	NA	NA
11. England, 2011	28/19	23/24	1m (0d-3.8y)	NA*	NA*	-	-	41	6	0	2	47	2	-	23	10	14	NA	NA	100%	100%	4.4y (1m-10y)
12. Saula, 2012	7/5	NA	NA	12	2	-	2	NA			-	12	2	-	NA			NA	NA	92%	100%	5-10y
Total	**159/108**	**114/128**	**Range 0d-2.3m**	**125**	**31**	**18**	**23**	**208**	**42**	**1**	**9**	**292**	**50**	**9**	**91**	**23**	**96**	**16/52**	**7/13**	**94%**	**95%**	**Range 3.5-5.8y**

Abbreviations AM: abdominal mass, BM: bone marrow, Ce: cellular type, Cl: classic type, d:days, EFS: event free survival, F: female, HC: hypercalciaemia, HE: hematuria, HT: hypertension, L: left, M: male, M: mixed type, m: months, NA: not available, NB: newborn, OS: overall survival, PH: polyhydramnion mother, P-CT: post-operative chemotherapy, Pr-CT: pre-operative chemotherapy, R: right, RT: radiotherapy, S: surgery, y: years

¶ Cook et al (1988) and Malone et al (1989) described the same series of CMN patients with different endpoints

Suspected malignant cells in bone marrow, no histological confirmation of CMN

* Symptom reported, number of patients unknown

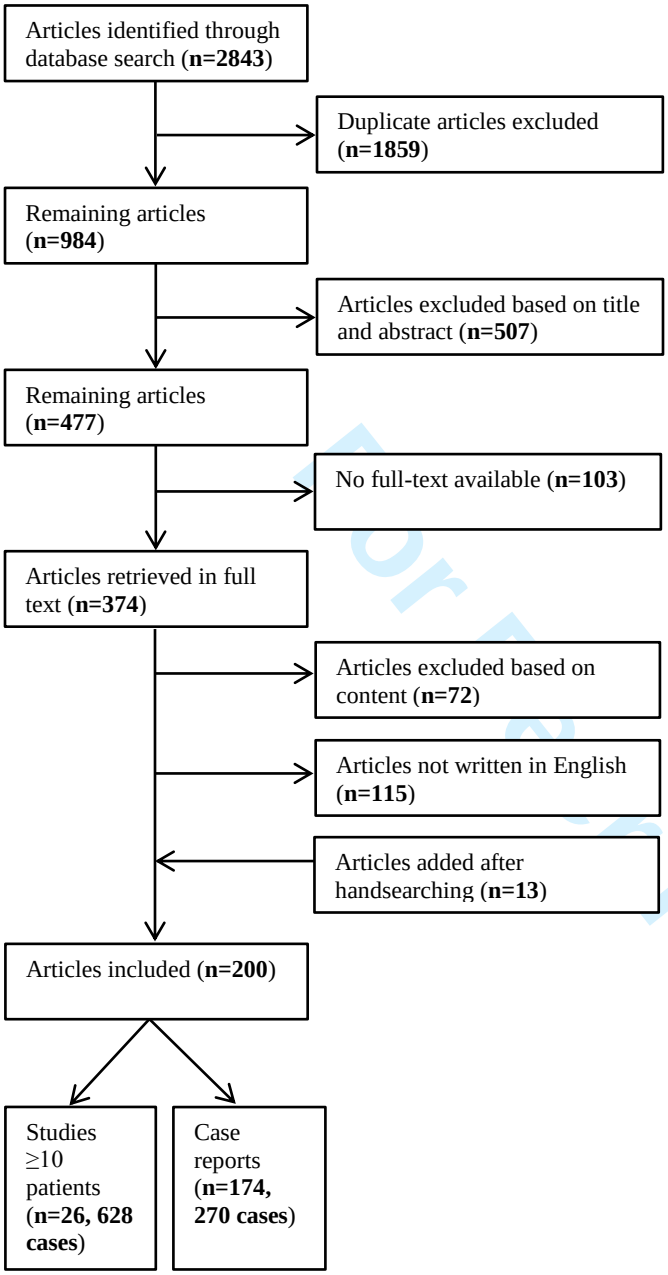
† Mean follow-up instead of median follow-up

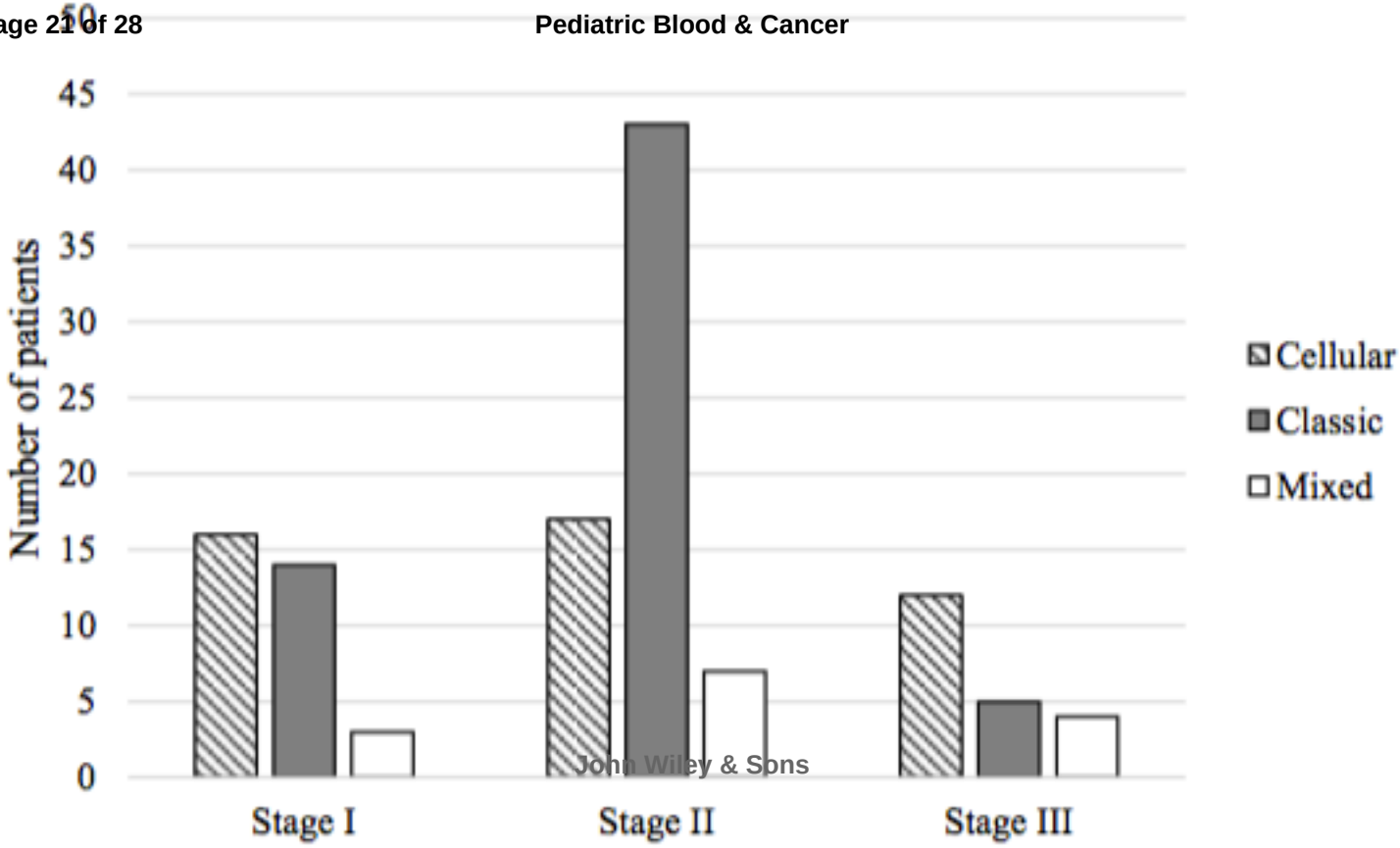
Table 2. Stage, histology and outcome of reported CMN cases harboring t(12;15)(p13;q22) or trisomy 11

	t(12;15)(p13;q22) *		Trisomy 11 *	
	Series ≥ 10 patients	**Case reports ****	**Series ≥ 10 patients**	**Case reports ****
Number of cases analyzed	65	NA	13	NA
Number of positive cases	19	16	7	15
Stage	I/II: 3 III: 1 Unknown: 15	I/II: 5 III: 4 Unknown: 7	I/II: 0 III: 0 Unknown: 7	I/II: 7 III: 2 Unknown: 6
Histology	Classic: 0 Mixed: 0 Cellular: 19 Unknown: 0	Classic: 0 Mixed: 4 Cellular: 10 Unknown: 2	Classic: 0 Mixed: 0 Cellular: 7 Unknown: 0	Classic: 0 Mixed: 3 Cellular: 9 Unknown: 3
Outcome data available	n = 13	n = 5	n = 7	n = 4
Outcome	Relapse: 2/13 Dead of disease: 1/13	Relapse: 2/5 Dead of disease: 0/5	Relapse: 0/7 Dead of disease: 0/7	Relapse: 0/4 Dead of disease: 0/4

***** Six cases described in series ≥ 10 patients and 11 cases described in case reports harbored both t(12;15)(p13;q22) and trisomy 11

** Case reports also included in series ≥ 10 patients were removed from this table





Supplemental Table S1. Available series reporting ≥ 10 CMN patients

Author, year	M/F	L/R	Median age (range)	Presenting symptoms				Stage			Treatment				Histologic patterns			Genetics		EFS	OS	Median follow-up (range)
				AM	HT	HE	Other	I/II	III	IV	Pr-CT	S	P-CT	RT	Cl	M	Ce	t(12;15)	Trisomy 11			
NON-OVERLAPPING SERIES																						
1. Howell, 1982	33/18	26/25	2.3m	48	2	9	6	39	12	0	-	51	28	4	NA			NA	NA	98%	98%	3.2y (4m-11.5y)
2. Sandstedt, 1985	11/18	13/16	NA	18	-	5	5	21	8	0	-	29	5	1	9	-	20	NA	NA	93%	93%	> 4y
3. Cook, 1988 / Malone, 1989 ¶	9/3	3/9	3d (1d-2.5y)	11	4	1	NA*	11	1	0	-	12	1	-	NA			NA	NA	83%	83%	7.3y †
4. Barrantes, 1991	8/5	9/4	0d (0d-19m)	NA*	-	-	-	12	0	1 #	-	13	4	3	9	1	3	NA	NA	85%	85%	5.8y
5. Leclair, 2005	NA	NA	NA	NA				25	1	0	-	26	-	-	21		5	NA	NA	96%	96%	±3.5y
6. Anderson, 2006	NA	NA	2m (0d-11m)	NA				11	2	0	-	13	-	-	3	6	4	3/13	NA	85%	100%	NA
7. Furtwaengler, 2006	34/16	21/29	18.5d (0d-2.6y)	27	16	1	6	41	9	0	5	50	6	1	29	-	21	NA	NA	94%	95%	4.2y (0.8-8.3y)
8. Watanabe, 2007	7/6	NA	30d (5d-7m)	NA				NA			NA				4	1	8	8/12	7/13	92%	92%	NA
9. Bayindir, 2009	7/3	5/5	3.1m (6d-5.5m)	9	7	2	4	7	3	0	2	9	2	-	2	2	6	2/10	NA	70%	90%	3.6y (6m-7y) †
10. Chaudry, 2009	15/15	14/16	NA	NA*	-	-	-	NA			NA	30	NA	NA	12	3	15	6/30	NA	93%	NA	NA
11. England, 2011	28/19	23/24	1m (0d-3.8y)	NA*	NA*	-	-	41	6	0	2	47	2	-	23	10	14	NA	NA	100%	100%	4.4y (1m-10y)
12. Saula, 2012	7/5	NA	NA	12	2	-	2	NA			-	12	2	-	NA			NA	NA	92%	100%	5-10y
Total	**159/108**	**114/128**	**Range 0d-2.3m**	**125**	**31**	**18**	**23**	**208**	**42**	**1**	**9**	**292**	**50**	**9**	**91**	**23**	**96**	**16/52**	**7/13**	**94%**	**95%**	**Range 3.5-5.8y**
PARTIALLY OVERLAPPING SERIES																						
Bogdan, 1973 ^[1]	14/5	NA	4w (0d-2.5y)	15	-	-	4	NA			2	15	5	8	NA			NA	NA	68%	68%	1.8y (0m-34y)
Shen, 1980 ^[1]	5/5	7/3	5d (1d-8m)	10	1	2	1	NA			-	10	4	-	5	3	2	NA	NA	90%	90%	4.5y (3.3-10y)
Snyder 1980 ^[1]	8/3	NA	0d(0d-6m)	NA*			3	11	0	0	-	11	-	5	9	-	2	NA	NA	73%	73%	NA (3-26y)
Hartman, 1981 ^[1]	9/11	NA	2w (0d-16y)	NA				NA			NA				NA			NA	NA	NA	NA	NA
Chan, 1987 ^[1]	9/8	NA	Cl:5.3d (1-21d) Ce:5.3m (1-18m)	NA*	14	3	6	17	0	0	-	17	3	2	9	8		NA	NA	100%	100%	10y †
Pettinato, 1989 ^[1]	7/9	9/4	Cl: 16d M:2.3m Ce:5.3m	NA*	2	2	3	15	1	0	0	14	1	-	6	3	7	NA	NA	81%	81%	5.3y †
Schofield, 1993 ^[1]	8/9	NA	7d (1d-2y)	NA				NA			0	17	5	-	6	5	5	NA	7/17	88%	88%	Range 8m-22y
Mascarello, 1994 ^[1,10]	NA	NA	NA	NA				NA			NA				11	12		NA	9/23	NA	NA	NA
O'Malley, 1996 ^[1]	9/6	NA	NA(2d-2y)	NA				NA			-	15	1	-	1	6	9	NA	NA	NA	NA	NA
Knezevich, 1998 ^[9,10]	8/7	NA	1m (1d-3y)	NA				NA			NA				4	2	9	10/15	9/14	NA	NA	NA
Shao, 2004 ^[1,9,10]	NA	NA	NA	NA				NA			NA				5	-	7	NA	NA	NA	NA	NA
Abosoudah, 2008 ^[10]	8/6	NA	12d (3d-2y)	NA*	-	-	-	NA			NA				4	1	9	9/10	NA	86%	93%	NA
Vd Heuvel-Eibrink, 2008 ^[7]	NA	NA	< 7m	NA				98	17	0	NA				NA			NA	NA	94%	96%	NA

Abbreviations AM: abdominal mass, BM: bone marrow, Ce: cellular type, Cl: classic type, d:days, EFS: event free survival, F: female, HC: hypercalciaemia, HE: hematuria, HT: hypertension, L:left, M: male, M: mixed type, m: months, NA: not available, NB: newborn, OS: overall survival, PH: polyhydramnion mother, P-CT: post-operative chemotherapy, Pr-CT: pre-operative chemotherapy, R: right, RT: radiotherapy, S: surgery, y: years

^ Overlap of patients with other series (number of overlapping series is depicted, for example ^[1] means overlap with the study by 1. Howell, 1982)

¶ Cook et al (1988) and Malone et al (1989) described the same series of CMN patients with different endpoints

Suspected malignant cells in bone marrow, no histological confirmation of CMN

* Symptom reported, number of patients unknown

† Mean follow-up instead of median follow-up

Supplemental Table S2. CMN patients described in case reports

Study (year)	Sex	Age at diagnosis	Side	Presenting symptoms	Conginital abnormalities	Tumour rupture	Operative procedures	Overall stage	Histological type	Volume at diagnosis	Genetics	Event-free survival (status)	Overall survival (status)	Overall survival (months)	Cause of death
Adem -1 (2001)	M	NA	NA	NA	NA	NA	NA	NA	Cellular	NA	t(12;15)(p13;q25), trisomy 11	NA	NA	NA	NA
Adem -2 (2001)	NA	NA	NA	NA	NA	NA	NA	NA	Classic	NA	NA	NA	NA	NA	NA
Al-Turkistani (2008)	F	PN: GA 26 w	R	Fetal abdominal mass*, polyhydramnios*	No	NA	Total nephrectomy 4 weeks after birth	NA	Mixed	4x5x4,5cm	NA	NA	NA	NA	NA
Ali (1994)	M	PN: GA NA	L	Fetal abdominal mass*	NA	NA	Total nephrectomy 3 days after birth	NA	Cellular	NA	NA	Relapse	Died	9	Tumor progression
Angulo (1991)	M	14 D	R	Congenital hypertrophic pyloric stenosis, renal tumor found during pyloromyotomy	NA	No	Total nephrectomy	I	Cellular	NA	NA	No relapse	Alive	108	.
Angulo (1991)	M	PN: GA 37 w	R	Stillborn	No	NA	No surgery (stillborn)	NA	Classic	NA	NA	Stillborn	Died	0	Stillborn (hydrops fetalis)
Anunobi (2014)	F	0 D (NB)	L	Stillborn, abdominal mass, polyhydramnios*	NA	NA	No surgery	NA	Classic	5x5x3cm	NA	Died	Died	1 day	Patient died due to complications of prematurity, tumor found at
Arensman (1980)	M	4 D	L	Left flank mass	No	Yes	Total nephrectomy	III	NA	NA	NA	No relapse	Alive	24	.
Argani -1 (2000)	M	14 Mo	NA	NA	NA	NA	Tumor resection (total nephrectomy?)	II	Cellular	NA	t(12;15)(p13;q25)	Relapse	Alive	84	.
Argani -2 (2000)	M	11 Mo	NA	NA	NA	NA	Total nephrectomy	NA	Cellular	980 gram	t(12;15)(p13;q25)	NA	NA	NA	NA
Bandyopadhyay -1 (2009)	F	3 Mo	NA	Abdominal mass	NA	NA	Total nephrectomy	I	Classic	8,5x5x4cm	NA	No relapse	Alive	24	.
Bandyopadhyay -2 (2009)	M	2.5 Mo	NA	Abdominal mass	NA	NA	Total nephrectomy	I	Classic	9x6x4cm	NA	No relapse	Alive	24	.
Bandyopadhyay -3 (2009)	F	3 Mo	L	Abdominal mass, vomiting	NA	NA	Total nephrectomy	I	Cellular	8x5x4cm	NA	No relapse	Alive	24	.
Bauer (1979)	F	3 Mo	R	Abdominal distention, vomiting, diarrhea, hyperreninemia	NA	NA	Total nephrectomy	II	NA	9.5cm (diameter)	NA	No relapse	Alive	18	.
Becroft (1995)	F	1 Mo	L	Abdominal mass	No	NA	Tumor resection (total nephrectomy?)	II	Mixed	8x7x5.5cm	54XX, +del(1)(p13), trisomy 2/7/8/12/15/17, biallelic expression	No relapse	Alive	48	.
Bell (2002)	F	9 Mo	R	Low-grade fever, abdominal distension, diarrhoea, general malaise	No	NA	Partial resection (infiltration duodenum and colon)	III	Mixed	16x6x7cm	NA	Relapse	NA	NA	NA
Bendre -1 (2014)	M	2 Mo	R	Abdominal mass	NA	No	Total nephrectomy	NA	Classic	9.3x3x3cm	NA	No relapse	Alive	22	.
Bendre -2 (2014)	M	3 Mo	R	Abdominal mass, hypertension	NA	No	Total nephrectomy	NA	Classic	NA	NA	No relapse	Alive	24	.
Bernstein (1994)	F	5 w	L	Abdominal distention, crying, decreased appetite	No	NA	Nephrectomy (95% of the tumor removed)	III	Cellular	14x10x6cm	50XX, +der(6)del(6)(p23) add (6)(q11), trisomy 8/10/11, add(12)(p130)	NA	NA	NA	NA
Bisceglia (2000)	F	0 D (NB)	R	Abdominal mass	No	NA	Total nephrectomy 1 month after birth	II	Classic (with some features - high mitotic index- of cellular variant)	3cm (diameter)	Flow cytometry: euploid DNA content	No relapse	Alive	72	.
Blank -1 (1978)	M	0 D (NB)	R	Abdominal mass, polyhydramnios*, premature delivery at 32 weeks gestation	No	NA	Total nephrectomy 4 days after birth	NA	NA	NA	NA	No relapse	Alive	6	.
Blank -2 (1978)	M	0 D (NB)	R	Abdominal mass, polyhydramnios*	No	NA	Total nephrectomy (timing unknown)	NA	NA	NA	NA	Died	Died	0	Fatal tear in inferior vena cava during nephrectomy
Blank -3 (1978)	F	0 D (NB)	R	Abdominal mass, polyhydramnios*	NA	NA	Total nephrectomy 8 days after birth	NA	NA	NA	NA	No relapse	Alive	12	.
Bolande -1 (1967)	M	0 D (NB)	R	Abdominal mass, transient hyperbilirubinaemia	NA	NA	Total nephrectomy 1 week after birth	NA	NA	NA	NA	No relapse	Alive	72	.
Bolande -2 (1967)	F	0 D (NB)	L	Abdominal mass	NA	NA	Total nephrectomy 5 days after birth	NA	NA	NA	NA	No relapse	Alive	12	.
Bolande -3 (1967)	F	0 D (NB)	NA	Abdominal mass, respiratory distress, sepsis, hyperbilirubinaemia	NA	NA	Total nephrectomy 3 weeks after birth	NA	NA	NA	NA	No relapse	Alive	72	.
Bolande -4 (1967)	M	3 Mo	R	Abdominal mass	NA	NA	Total nephrectomy	NA	NA	NA	NA	No relapse	Alive	72	.
Bolande -5 (1967)	F	0 D (NB)	R	Abdominal mass	NA	NA	Total nephrectomy 2 days after birth	NA	NA	NA	NA	Died	Died	0.4	Pseudomonas sepsis on 12th post-operative day
Bolande -6 (1967)	F	0 D (NB)	L	Abdominal mass	NA	NA	Total nephrectomy in first week after birth	NA	NA	NA	NA	No relapse	Alive	60	.
Bolande -7 (1967)	M	0 D (NB)	R	Abdominal mass	NA	NA	Total nephrectomy in first week after birth	NA	NA	NA	NA	No relapse	Alive	36	.
Bolande -8 (1967)	F	0 D (NB)	L	Abdominal mass	NA	NA	Total nephrectomy 2 months after birth	NA	NA	NA	NA	No relapse	Alive	180	.
Campagnola (1998)	M	4 Mo	L	Abdominal distention	NA	NA	Total nephrectomy	NA	Cellular	17x17cm	NA	No relapse	Alive	48	.
Campos (2001)	NA	0 D (NB)	R	Abdominal mass	NA	NA	Total nephrectomy 6 days after birth	I	Cellular	NA	NA	No relapse	Alive	24	.
Carpenter (1993)	F	PN: GA 36 w	L	Fetal abdominal mass*	NA	NA	Total nephrectomy (timing unknown)	I	Mixed	8x5x4,5cm	46X-X, t(12;15)(p13;q25), trisomy 11	No relapse	Alive	19	.
Celik (2009)	M	PN: GA 28 w	L	Fetal abdominal mass*, polyhydramnios*	NA	No	Total nephrectomy 3 days after birth	NA	Cellular	6x5,5x4,5cm	NA	NA	NA	NA	NA
Chan (1995)	F	3 D	R	Abdominal mass, vomiting	NA	No	Total nephrectomy	III	Cellular	6.5cm diameter	NA	No relapse	Alive	12	.
Chan -1 (2002)	NA	PN: GA 30 w	NA	Fetal abdominal mass*	NA	No	Total nephrectomy after 1 course of vincristine	NA	NA	NA	NA	No relapse	Alive	84	.

Supplemental Table S3. Immunohistochemical staining of 53 CMN patients described in case reports

Staining	Positive				Negative			
	Classic	Mixed	Cellular	NA	Classic	Mixed	Cellular	NA
Vimentin	7	5	17	3	1	2		
Desmin				3	3	2	9	2
(Smooth muscle) actin	3	3	5	3	2	1	5	
(Cyto)keratin	1		2		3	1	7	
S-100		1			2	1	3	
Neuronspecific enolase					1		1	
TrkC antibody			1					
Epithelial membrane antigen	3	3	3		2		7	
AE1/AE3	2	2	2		1	1	1	
PTHrP		1	1					
c-kit				2	1			
Ki-67	1		4		1			
CD34	1				2		4	
Myoglobin							1	
Alpha-fetoprotein							1	
Bcl-2							1	
CD99							1	
INI1			4					
Fibronectin	1	1	2					
Laminin					1	1	2	
TP					2	3	2	
PHA					3	2	2	
THP	1		1		1	2	1	
AH	3	3	2					
PSA	1	1	1		2	2	1	
WT1-GP			1	1				
Renin								1

Supplemental Table S4. Characteristics and treatment of reported deceased CMN patients

Type of report	Report	Age	Stage	Histologic subtype	Tx at diagnosis	Relapse	Cause of death
Series ≥ 10 patients	Furtwangler 2006	6m	III	Cellular	PN, CN (rupture)	Yes	Tumor progression
	Furtwangler 2006	2.7y	I	Cellular	Pre-op CT, CN, post-op CT	Yes	Tumor progression
	Bayindir 2009	3.9m	III	Cellular	Pre-op CT	No	Tumor progression
	Watanabe 2007	1.1y	II	Cellular	CN, post-op CT (NWTS-3 regimen K)	Yes	Tumor progression
	Leclair 2005	NB	I/II	Cellular	CN	No	Toxicity (surgery)
	Barrantes 1991	NB	II	Classic	CN, RT	Yes	Tumor progression
	Barrantes 1991	NB	II	Classic	CN	No	Toxicity (surgery)
	Howell 1982	NB	III	NA	CN (rupture), AMD	No	Toxicity (chemotherapy)
	Sandstedt 1985	NA	NA	NA	NA	No	Toxicity (surgery)
	Sandstedt 1985	NA	NA	NA	NA	No	Toxicity (surgery)
	Cook 1988 /Malone 1989	1d	III	NA	CN (rupture), post-op CT	No	Toxicity (chemotherapy)
	Cook 1988 /Malone 1989	3d	I/II	NA	CN	No	Toxicity (surgery)
Case reports	Ali 1994	NA	NA	Cellular	CN	Yes	Tumor progression
	Cheol 2007	NB	NA	Cellular	None	No	Tumor progression
	Jones 2007	1d	III	Cellular	CN	Yes	Tumor progression
	Joshi 1986	10m	III	Cellular	CN, post-op CT (AVD), RT	Yes	Tumor progression
	Santos 2011	2.8y	NA	Cellular	CN, post-op CT	Yes	Tumor progression
	Vujanic 1993	1.2y	III	Cellular	Surgery, post-op CT (AV)	Yes	Toxicity (chemotherapy)
	Angulo 1991	NB	I	Classic	None	No	Stillborn (hydrops fetalis)
	Chen 2003	NB	NA	Classic	None	No	Died directly after birth (hydrops fetalis)
	Anunobi 2014	NB	NA	Classic	None	No	Died 13 hours after birth (prematurity, polyhydramnios mother)
	Correia 1995	7m	I	Classic	CN	No	Toxicity (peritonitis due to peritoneal dialysis)
	Favara 1968	NB	NA	Classic	None	No	Died 8 hours after birth (respiratory distress)
	Kumar 1985	0m	NA	Classic	NA	NA	Toxicity (sepsis)
	Walker 1973	3m	NA	Classic	CN, post-op CT (ACT)	Yes	Tumor progression
	De Paepe 2011	NB	NA	Mixed	None	No	Intra-uterine death (intra-tumoral hemorrhage, early non-immune hydrops)
	Heidelberger 1993	NB	NA	Mixed	CN	Yes	Tumor progression
	Gray 1989	NB	NA	NA	None	No	Intra-uterine death (hydrops fetalis)
	Kotani 2010	NB	NA	NA	CN	No	Toxicity (surgery)
	Liu 1996	NB	NA	NA	None	No	Died directly after birth (ascites, pleural effusions, pericardial effusion, subcutaneous oedema)
	Meenal 2003	NB	NA	NA	None	No	Stillborn
	Blank 1978	NB	NA	NA	CN	No	Toxicity (surgery)
	Bolande 1967	NB	NA	NA	CN, post-op CT (ACT)	No	Toxicity (surgery)
	Larson 1978	NB	NA	NA	None	No	Tumor progression and advanced hyaline membrane disease
	Wigger 1969	NB	NA	NA	CN	No	Toxicity (surgery)
	Wigger 1969	NB	NA	NA	CN	No	Toxicity (surgery)

Abbreviations CN: complete nephrectomy, NA: not available, NB: newborn, PN: partial nephrectomy, post-CT: post-operative chemotherapy, pre-op CT: pre-operative chemotherapy, Tx: treatment

Supplemental Table S5. Characteristics, treatment and outcome of reported relapsed CMN patients

Source	Report	Age	Stage	Histologic subtype	Initial treatment	Time to relapse	Location of relapse	Treatment of relapse	Outcome (follow-up time)
Series ≥ 10 patients	Furtwaengler 2006	3m	III	Cellular	CN (rupture)	NA	Local	S, CT (AVD)	Alive (5.6y)
	Furtwaengler 2006	6m	III	Cellular	PN, CN (rupture)	NA	Local	CT (AVI)	Died of tumor progression (1y)
	Furtwaengler 2006	2.7y	I	Cellular	Pre-op CT, CN, post-op CT	NA	Local	CT (ICED), RT, S	Died of tumor progression (1.5y)
	Bayindir 2009	5m	III	Cellular	Pre-op CT (AV), CN (incomplete), post-op CT (AV)	2m	Local	S, CT (VCD/VP-16/IFO), RT	Alive (7y)
	Chaudry 2009	NA	NA	Cellular	CN	<6m	Local	NA	NA
	Chaudry 2009	NA	NA	Cellular	CN	<6m	Local	NA	NA
	Watanabe 2007	1.1y	II	Cellular	CN, post-op CT (NWTS-3 regimen K)	NA	Bone (ilium, humerus, vertebrae)	NA	Died of tumor progression (1.3y)
	Anderson 2006	NB	III	Cellular	CN	6m	Local	S, CT (VCR/IFO/ACT)	Alive (NA)
	Barrantes 1991	NB	II	Classic	CN, RT	NA	NA	None	Died of tumor progression (9m)
	Bayindir 2009	3m	II	Mixed	CN	6m	Lung	S, CT (VCD)	Alive (4.5y)
	Anderson 2006	8m	III	Mixed	CN	8m	Local	S, CT (AVD+ICE)	Alive (NA)
	Howell 1982	4m	NA	NA	CN (spill), AV	7m	Local	S, CT (DOX/CYC)	Alive (1.6y)
Case reports	Ali 1994	NB	NA	Cellular	CN	3m	Local, brain	S, CT (type NA)	Died of tumor progression (9m)
	Jones 2007	NB	III	Cellular	CN	6m	Local	S	Alive (7m)
	Argani 2000	1.2y	II	Cellular	S (type unknown)	12m	Lung	S	Alive (7y)
	Glick 2004	3.5m	II	Cellular	CN	6m	Lung	S, CT (type NA)	Alive (6m)
	Gonzalez-Crussi 1980	7m	NA	Cellular	CN	3m	Lung	S, RT, CT (ACT)	Alive (5.5y)
	Jones 2007	1d	III	Cellular	CN (rupture)	6m	Local	S, CT (AVD/CYC/CIS)	Died of tumor progression (1.6y)
	Joshi 1986	10m	III	Cellular	CN, post-op CT (AVD), RT	13m	Local	S, CT (AVD)	Died of tumor progression (1.6y)
	Loeb 2002	1y	III	Cellular	CN (rupture)	3m	Local	CT (AVD), RT	Alive (18y)
	Loeb 2002	3m	III	Cellular	CN (rupture), post-op CT (AVD)	5m	Local	CT (IFO/CARBO/VP-16), RT	Alive (9y)
	Loeb 2002	NB	III	Cellular	CN (rupture)	5m	Local	S, CT (VCD)	Alive (2y)
	Patel 2003	9m	II	Cellular	Pre-op CT (AV), CN	2.5m	Liver	CT (VCR/IFO/DOX/VP-16), S	Alive (1.5y)
	Santos 2011	2.8y	NA	Cellular	S (type unknown), post-op CT (type NA)	8m	Local	S, CT (type NA)	Died of tumor progression (1.2y)
	Steinfeld 1984	4m	NA	Cellular	CN	2m	Local, lung	CT (AVD/CYC), RT, S	Alive (1.6y)
	Vujanic 1993	1.2y	III	Cellular	S (type unknown), post-op CT (AV)	5m	Lung, heart	S, CT (IFO/VCR)	Died of pneumonia (2y)
	Wang 2014	1.5m	I	Cellular	TE	8m	Local	CT (AVD), S	Alive (4y)
	Walker 1973	3m	NA	Classic	CN, post-op CT (ACT)	4m	Local	S, RT	Died of tumor progression (4m)
	Heidelberger 1993	NB	NA	Mixed	CN	7m	Brain	S, CT (type NA)	Died of tumor progression (14m)
	Ko 2013	NB	III	Mixed	CN	7w	Local, liver	CT (AVC)	Alive (7m)
	Bell 2002	9m	III	Mixed	Pre-op CT, PN, post-op CT	3m	Liver	S, CT (type NA)	NA
	Joshi/Fu 1973	1d	III	NA	CN	4m	Local	RT, CT (AV)	Alive (15m)

Abbreviations ACT: actinomycin, AVC: actinomycin/vincristine/cyclophosphamide, AVD: actinomycin/vincristine/doxorubicin, AVI: actinomycin/vincristine/ifosfamide, CIS: cisplatin, CN: complete nephrectomy, CT: chemotherapy, CYC: cyclophosphamide, DOX: doxorubicin, ICE: ifosfamide/carboplatin/etoposide, ICED: ifosfamide/cyclophosphamide/etoposide/doxorubicin, IFO: ifosfamide, m: months, NA: not available, NB: newborn, RT: radiotherapy, S: surgery, TE: tumor enucleation, VCD: vincristine/cyclophosphamide/doxorubicin, VCR: vincristine, VP-16: etoposide, y: years

Supplemental Table S6. Characteristics, treatment and outcome of reported stage III CMN patients

Type of report	Study	Age	Gender	Histology	Initial therapy	Reason for stage III	Relapse	Relapse treatment	Outcome
Series ≥ 10 patients	Furtwaengler 2006	3m	Female	Cellular	CN	Tumor rupture	Yes (local)	Surgery, AVD	Alive (5.6y)
	Furtwaengler 2006	3m	Female	Cellular	PN. 2nd look surgery, CN, post-op CT	Margin+, tumor rupture	No	-	Alive (7.2y)
	Furtwaengler 2006	6m	Female	Cellular	PN. 2nd look surgery, CN	Margin+, tumor rupture	Yes (local)	AVI	DOD (1y)
	Furtwaengler 2006	8m	Female	Cellular	CN, 2nd look surgery, post-op CT	Margin+, tumor rupture	No	-	Alive (5.8y)
	Furtwaengler 2006	2y	Female	Cellular	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (1.9y)
	Bayindir 2009	4m	Female	Cellular	Biopsy, pre-op CT (AV), CN (incomplete), post-op CT (AV)	Margin+	Yes (local, liver)	Surgery, VCD+VP-16/IFO, RT (10.5 Gy)	Alive (7y)
	Anderson 2006	NB	NA	Cellular	CN	Tumor rupture	Yes (local)	Surgery, VCR+ACT+IFO	Alive (NA)
	Bayindir 2009	2m	Male	Cellular	CN, post-op CT	Margin+	No	-	Alive (2.5y)
	Bayindir 2009	3m	Male	Cellular	Biopsy, pre-op CT	Margin+	No	-	DOD (6m)
	England 2011	NB	NA	Cellular	CN	Margin+, tumor rupture	No	-	Alive (4y)
	England 2011	2d	NA	Cellular	CN	Margin+	No	-	Alive (1.2y)
	Leclair 2005	NA	NA	Classic	CN	Tumor rupture	No	-	Alive (2y)
	Furtwaengler 2006	NB	Male	Classic	CN	Margin+	No	-	Alive (2.2y)
	Furtwaengler 2006	1w	Female	Classic	CN	Margin+	No	-	Alive (2.7y)
	Furtwaengler 2006	2w	Female	Classic	CN	Margin+	No	-	Alive (2.4y)
	Furtwaengler 2006	3m	Female	Classic	PN, 2nd look surgery, CN	Margin+	No	-	Alive (1.1y)
	England 2011	7w	NA	Classic	CN	Margin+	No	-	Alive (5.3y)
	Anderson 2006	8m	NA	Mixed	CN	Tumor rupture	Yes (local)	Surgery. AVD+ICE	Alive (NA)
	England 2011	1d	NA	Mixed	CN	Margin+	No	-	Alive (2.2y)
	England 2011	2d	NA	Mixed	CN	Margin+	No	-	Alive (2y)
	England 2011	11m	NA	Mixed	CN, post-op CT	Tumor rupture	No	-	Alive (5.4y)
	Howell 1982	1d	NA	NA	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (2.5y)
	Howell 1982	2d	NA	NA	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (6.5y)
	Howell 1982	2d	NA	NA	CN, post-op CT	Tumor rupture	No	-	Died of sepsis (2w)
	Howell 1982	3w	NA	NA	CN	Tumor rupture	No	-	Alive (1.5y)
	Howell 1982	3w	NA	NA	CN	Tumor rupture	No	-	Alive (1.7y)
	Howell 1982	1m	NA	NA	CN	Margin+, tumor rupture	No	-	Alive (2.2y)
	Howell 1982	4m	NA	NA	CN, post-op CT, RT	Margin+, tumor rupture	No	-	Alive (2.5y)
	Howell 1982	4m	NA	NA	CN, post-op CT	Margin+, tumor rupture	No	-	Alive (5.5y)
	Howell 1982	4m	NA	NA	CN, post-op CT	Margin+, tumor rupture	Yes (local)	Surgery, CYC/ADR	Alive (2.2y)
	Howell 1982	5m	NA	NA	CN, post-op CT	Margin+	No	-	
	Howell 1982	16m	NA	NA	CN, post-op CT, RT	Margin+	No	-	
	Howell 1982	9y	NA	NA	CN, post-op CT, RT	Tumor rupture	No	-	
	Cook 1988/Malone 1989	3d	Male	NA	CN, post-op CT	Tumor rupture	No	-	Died of sepsis (3w)
Case reports	Jayabose 1988	2m	Female	Cellular	CN, AVD	Margin+	No	-	Alive (1.8y)
	Jones 2007	1d	Female	Cellular	CN	Margin+	Yes (local)	Surgery, AVCD + cisplatin	DOD (1.5y)
	Joshi 1986	10m	Male	Cellular	CN, AVD, RT	Margin+	Yes (local)	Surgery, continuation AVD	DOD (1.5y)

	Matsumara 1993	NB	Male	Cellular	CN	Tumor rupture	No	-	Alive (2y)
	Jones 2007	NB	Female	Cellular	CN	Margin+	Yes (local)	Surgery	Alive (7m)
	Chan 1995	3d	Female	Cellular	CN, VCR	Surgical biopsy	No	-	Alive (1y)
	Gormley 1989	2m	Female	Cellular	CN, AV	Tumor rupture	No	0	Alive (9m)
	Kalidasan 1994	5m	Male	Cellular	CN	Tumor rupture	No	-	Alive (7y)
	Kelly 1985	8m	Female	Cellular	CN, AV	Tumor rupture	No	-	Alive (11m)
	Loeb 2002	12m	Female	Cellular	CN	Tumor rupture	Yes (local)	AVD, RT	Alive (18y)
	Loeb 2002	3m	Female	Cellular	CN, AVD	Tumor rupture	Yes (local)	ICE, RT	Alive (9y)
	Loeb 2002	NB	Female	Cellular	CN	Tumor rupture	Yes (local)	Surgery, VCD	Alive (2y)
	McCahon 2003	NB	Female	Cellular	AVC	Surgical biopsy	No	-	Alive (2.5y)
	Vujanic 1993	14m	Female	Cellular	CN, AV	Margin+	Yes (lungs, heart)	Surgery, IV	Died of pneumonia (2y)
	Whittle 2010	NB	Female	Cellular	CN	Surgical biopsy	No	-	Alive (1y)
	Irsutti 2000	NB	Male	Classic	CN	Margin+	No	-	Alive (10m)
	Walterhouse 1990	2d	Male	Classic	CN	Margin+	No	-	Alive (2y)
	Bell 2002	9m	Female	Mixed	Pre-op CT, CN, post-op CT	Margin+	Yes (liver)	Surgery, CT (type unknown)	
	Arensman 1980	4d	Male	NA	CN	Tumor rupture	No	-	Alive (2y)
	Ehman 1983	NB	Male	NA	CN	Margin+	No	-	Alive (1y)
	Goldberg 1994	5m	Male	NA	CN	Tumor rupture	No	-	Alive (1y)
	Joshi/Fu 1973	1d	Female	NA	CN	Margin+	Yes (local)	Surgery, AV	Alive (12.5y)

Abbreviations ADR: adriamycin**,** AV: actinomcyin/vincristine, AVC: actinomycin/vincristine/cyclophosphamide, AVCD: actinomycin/vincristine/cyclophosphamide/doxorubicin, AVD: actinomycin/vincristine/doxorubicin, CN: complete nephrectomy, CT: chemotherapy, CYC: cyclopohspahmide, DOD: died of disease (tumour progression), ICE: ifosfamide/carboplatin/etoposide, IV: ifosfamide/vincristine, NB: newborn, PN: partial nephrectomy, post-op CT: post-operative chemotherapy, pre-op CT: pre-operative chemotherapy, VCD: vincristine/cyclophosphamide/doxorubicin, VCR: vincristine, VIE: vincristine/ifosfamide/etoposide