







## BRIEF REPORT

# Malignant ectomesenchymoma in children: The European pediatric Soft tissue sarcoma Study Group experience

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## Abstract

Malignant ectomesenchymoma (MEM) is an extremely rare soft tissue tumor typical of young children, currently included in the category of skeletal muscle malignancies and characterized by a neuroblastic component. This study describes a series of 10 patients prospectively registered in the European paediatric Soft tissue sarcoma Study Group (EpSSG) database. Of the 10 cases, seven had an initial local diagnosis of rhabdomyosarcoma. All patients received chemotherapy according to rhabdomyosarcoma strategy, four had radiotherapy. Overall, six patients were alive in first remission, two in second remission and one after second tumor. Only the patient with initially metastatic tumor died of disease.

## KEYWORDS

children, EpSSG, malignant ectomesenchymoma, outcome, treatment

**Abbreviations:** EFS, event-free survival; EpSSG, European paediatric Soft tissue sarcoma Study Group; IRS, Intergroup Rhabdomyosarcoma Study; MEM, Malignant ectomesenchymoma; NRSTS, non-rhabdomyosarcoma soft tissue sarcomas; OS, overall survival; RMS, rhabdomyosarcoma; TNM, tumor-nodes-metastases.

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## 1 | INTRODUCTION

Malignant ectomesenchymoma (MEM) is an extremely rare soft tissue tumor whose histogenesis has been debated over the years.

Originally considered a malignancy derived from neural crest, it is now included in the category of skeletal muscle malignancies. However, the diagnostic criteria for MEM have remained unchanged over the classifications. The current WHO classification for soft tissue tumors identifies as essential diagnostic criteria for MEM the histologic evidence of embryonal rhabdomyosarcoma (RMS) areas intermixed with a neuroblastic component (neurons, ganglioneuroma, ganglioneuroblastoma, or neuroblastoma), confirmed by positive immunostaining for desmin/myogenin and synaptophysin.<sup>1</sup> Although only few cases have been molecularly investigated, the evidence of *HRAS* pathogenic variants highlighted in a small series, together with clinical findings and response to therapeutic strategies used for RMS, support the hypothesis that MEM might have a histogenetic relationship with RMS.<sup>2</sup>

MEM characteristically occurs in the first 2 years of life and generally has aggressive clinical behavior.<sup>3,4</sup> The best treatment approach remains to be defined, in particular, the role of systemic therapy: discussions remain if chemotherapy should be directed against the mesenchymal or the neuroectodermal component.

The aim of this study is to describe the clinical findings of a series of pediatric patients with a diagnosis of MEM prospectively registered in European paediatric Soft tissue sarcoma Study Group (EpSSG) protocol dedicated to non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

## 2 | METHODS

The analysis was based on all patients registered within the EpSSG NRSTS 2005 study (European Union Drug Regulating Authorities Clinical Trials [EUDRACT] No. 2005-001139-315). The EpSSG NRSTS 2005 study (2005–2016) involved 100 enrolling academic centers and hospitals from 14 different countries, and included two prospective, nonrandomized, historically controlled trials (for localized adult-type NRSTS and for localized synovial sarcoma) and clinical recommendations for other histotypes including MEM.<sup>5</sup>

For the current analysis, inclusion criteria were (i) a pathologically proven diagnosis of MEM; (ii) age under 21 years; (iii) no previous treatment except for primary surgery; (iv) no pre-existing illness preventing treatment; (v) no previous malignant tumors; and (vi) written consent for inclusion in the study.

Tumor stage was assigned according to the clinical tumor-nodes-metastases (TNM) pre-treatment staging system<sup>6</sup> and the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping system.<sup>7</sup>

EpSSG NRSTS 2005 recommendations suggested treating patients with MEM following therapeutic guidelines adopted for high-risk RMS rhabdomyosarcoma, that is, chemotherapy with ifosfamide, vincristine, actinomycin-D (IVA) or ifosfamide, vincristine, actinomycin-D, doxorubicin (IVADo), for nine courses, plus surgery and/or radiotherapy according to the risk of local failure.<sup>8,9</sup>

For the current descriptive analysis, 5-year overall survival (OS) and event-free survival (EFS) of the whole population were calculated. OS was defined as time from start of treatment to death from any cause or last follow-up for patients alive. EFS was defined as time from start

of treatment to first failure (disease progression, relapse, secondary malignancy or death from any cause), whichever occurred first. Data cut off was at June 10, 2022.

## 3 | RESULTS

Between May 31, 2005 and Dec 31, 2016, 1321 patients were recruited in the EpSSG NRSTS 2005 study. Among them, nine had a diagnosis of localized MEM (0.8%). One additional case with metastatic disease was registered but not considered eligible (for the presence of metastases). The current cohort included therefore 10 patients, six males, four females with age range 4 months–6 years (median 17 months). All cases underwent international and/or national central histological review by EpSSG pathology panel. Fusion status was available for all cases: all were negative for FOXO1.

Of the 10 cases, only three had an initial local diagnosis of MEM. In the other cases, the initial local diagnosis was RMS (five embryonal, one alveolar, one spindle cells RMS) and diagnosis was modified to MEM after central review. Histologically, all MEM but one showed a predominant morphology of embryonal RMS with scattered areas characterized by isolated mature ganglion cells or in small clusters within a context of slender elongated cells with nuclei typical of Schwann cells. Immunostains for S100 and synaptophysin highlighted the schwannian component and ganglion cells, respectively. In two cases, scattered synaptophysin positive cells with a more immature morphology, difficult to distinguish from primitive rhabdomyoblastic cells, had led to interpretation of it as an aberrant expression of neuroectodermal markers in an RMS in absence of evident ganglion cells. The elongated slender cells, representing Schwann cells, had led to the initial diagnosis of spindle cell RMS in one case. The only MEM originally diagnosed as alveolar RMS showed a focal solid alveolar pattern, with scattered neuroblast and immature ganglion cells. Neuroblastoma-like areas were absent in all cases.

Clinical characteristics and treatment modalities of the 10 patients are described in Table 1.

Genito-urinary site was the primary tumor site in six cases (three paratesticular, two bladder-prostate, one vagina). Two patients had regional nodal involvement, and one had pulmonary metastases.

Multi-modal treatment included chemotherapy in all cases and radiotherapy in four (one protontherapy). In the five patients with measurable disease, response to chemotherapy was as follows: three partial response and one progressive disease (unknown in one case).

At the time of the current analysis, six patients were alive in first remission. Two patients with initially localized disease had local/locoregional relapse and were salvaged with second-line therapy (Table 1). The patient with initially metastatic tumor died of disease. Finally, a patient with localized MEM developed secondary acute myeloid leukemia after 15 months off therapy: she was treated for the second tumor and she was alive in remission from both tumors at the time of this report. The patient was tested for underlying genetic predisposition, with negative results (in particular, the patient was negative for TP53).

**TABLE 1** Clinical characteristics and treatment modalities of the 10 patients

Pt#	Sex	Age	Tumor site	Initial diagnosis	Histology	Stage (TNM, IRS)	Chemotherapy	Local treatment	Outcome
1	F	4 months	Pelvis	ERMS	ERMS + scattered areas of ganglion cells within neuropil S100+	T2b N0 M0 IRS III	IVA PR to chemotherapy	Biopsy, delayed surgery	Alive in first remission
2	M	5 months	Paratesticular	ERMS	ERMS + scattered areas of ganglion cells within neuropil S100+	T1b N0 M0 IRS I	IVA	Initial surgery R0	Alive in first remission
3	M	7 months	Bladder-Prostate	ARMS	Solid alveoli scattered ganglion cells	T2b N0 M0 IRS III	IVA No data on response to chemotherapy	Biopsy, delayed surgery plus RXT (50.4 Gy)	Alive in first remission
4	M	17 months	Paratesticular	SpRMS	Spindle cell areas in ERMS with scattered ganglion cells	T1a N0 M0 IRS I	IVA	Initial surgery R0	Alive in first remission
5	F	13 months	Vagina	MEM	Small round cell component co-expressing both S100 and Myogenin	T1a N0 M0 IRS II	IVA	Initial surgery R1	Alive in first remission
6	M	2 years	Paratesticular	MEM	ERMS with scattered ganglion cells within schwannian component	T1a N0 M0 IRS I	IVA	Initial surgery R0	Alive in first remission
7	M	3 years	Abdominal wall	ERMS	ERMS with scattered ganglion cells within schwannian component	T1b N1 M0 IRS III	IVA No response to chemotherapy	Delayed surgery plus RXT (48 Gy) on primary tumor and regional lymph nodes, after progression	Primary tumor and nodal progression 3 months from diagnosis, alive in second remission 3 years from relapse, after chemotherapy (irinotecan-temozolamide, then vinorelbine and low-dose cyclophosphamide), surgery and radiotherapy
8	M	6 months	Bladder-Prostate	ERMS	ERMS with scattered ganglion cells within schwannian component	T3b N1 M1 IRS IV	IVADo plus bevacizumab PR to chemotherapy	Initial biopsy, delayed surgery	Progressive disease after 7 months, dead of disease 1.6 months from first diagnosis
9	F	4 years	Orbit	ERMS	ERMS with scattered ganglion cells within schwannian component	T2b N0 M0 IRS III	IVA PR to chemotherapy	Initial biopsy, delayed surgery plus RXT (protontherapy, 50.4 Gy)	Local relapse 8 months from diagnosis, alive in second remission 3 years from relapse, after chemotherapy (vincristine, irinotecan, temozolamide) and mutilating surgery (orbit exenteration)
10	F	6 years	Parotid gland	MEM	ERMS + scattered areas of ganglion cells within neuropil S100+	T3b N0 M0 IRS II	IVADo	Initial surgery (R1), RXT (50.4 Gy)	Secondary acute myeloid leukemia after 15 months off therapy; alive in remission from both tumors, more than 10 years after MEM

Abbreviations: ARMS, alveolar rhabdomyosarcoma; ERMS, embryonal rhabdomyosarcoma; F, female; IVA, ifosfamide, vincristine, actinomycin-D; IVADo, ifosfamide, vincristine, actinomycin-D, doxorubicin; IRS, Intergroup Rhabdomyosarcoma Study grouping system: group I—initial complete resection (also called R0 resection), group II—grossly resected tumors with suspected microscopic residual disease (R1), group III—macroscopic residual disease (R2) or biopsy only (unresected disease); M, male; PR, partial response; RXT, radiotherapy; SpRMS, spindle cell rhabdomyosarcoma; TNM, tumor-nodes-metastases; T1 or T2, depending on local invasiveness, and TA or TB, depending on tumor diameter  $\leq 5$  or  $> 5$ .

**TABLE 2** Comparison of the clinical characteristics of three series on malignant ectomesenchymoma, that is, the Intergroup Rhabdomyosarcoma Study (IRS), the Cooperative Weichteilsarkom Studiengruppe (CWS), and the European paediatric Soft tissue sarcoma Study Group (EpSSG) series

Series	Clinical findings	Treatment and outcome
Bouè DR, et al, 2000 IRS series; study period 1985–1996; 15 patients	8 males, 7 females; age 6 months–15 years; tumor sites: external genital 5 (four paratesticular, one vulva), 6 pelvis-abdomen (two uterus), 3 head-neck region, one limb stage: 2 N1, 2 N1M1	No data on treatment; five alive disease free five alive with disease (four lost at follow-up) five dead of disease
Dantonello TM, et al. 2013 CWS series; study period 1996–2009; six cases	three males, three females; age 3 months–13 years (median 6 months); tumor sites: 3 limbs, 2 trunk, 1 orbit; stage: 5 localised, 1 metastatic	Five of six had chemotherapy; three relapses, one dead of disease (the patient with initial M1 disease)
Current series EpSSG series; study period 2005–2016; 10 cases	Six males, for females; age 4 months–6 years (median 17 months); tumor sites: 6 genito-urinary sites (3 paratesticular, 2 bladder-prostate, 1 vagina), 2 head-neck region (1 orbit, 1 parotid gland), 1 pelvis, 1 abdominal wall stage: 1 N1, 1 N1M1	All had chemotherapy, 4 radiotherapy; six alive disease free two alive in second remission one alive after second malignancy one dead of disease (the patient with initial M1 disease)

Abbreviations: CWS, Cooperative Weichteilsarkom Studiengruppe; EpSSG - European paediatric Soft tissue sarcoma Study Group; IRS, Intergroup Rhabdomyosarcoma Study; M1 - distant metastases; N1 - regional lymph node metastases.

With a median follow-up of 83 months (range 16–148 months), 5-year EFS and OS were 63% and 91%, respectively.

## 4 | DISCUSSION

The current study described clinical findings, treatment and outcome of a series of pediatric patients with MEM prospectively registered in EpSSG NRSTS 2005 study.

Our study highlights the possibility that a subset of MEM are initially misdiagnosed and treated as RMS. In our series, seven out of 10 cases were originally diagnosed as RMS.

According to our experience, this tumor mainly occurred in young children, mainly arising at genito-urinary sites. With a multidisciplinary approach borrowed from the treatment of RMS, the overall outcome of patients with localized MEM was satisfactory, with two loco-regional relapses out of nine cases. Our study can be compared with previous published experiences, the IRS series (15 cases)<sup>4</sup> and the report from the Cooperative Weichteilsarkom Studiengruppe (CWS) (six cases).<sup>3</sup> Table 2 summarizes clinical features and outcomes of these cohorts.

More in-depth histological and molecular investigations are needed to better study the biphenotypic differentiation of MEM and the role of the different components. The largest series (15 cases, from the IRS), published before the advent of extensive molecular characterization of RMS, suggested the prognostic implication of the RMS component, with alveolar component carrying a worse prognosis.<sup>4</sup> Other reports suggested that the persistence of neuroectodermal component and its easier detection in surgical specimens might be related to a minor response to the treatment regimens for RMS.<sup>10</sup>

A better understanding of the tumorigenesis may help in defining the more adequate systemic treatment with the current available

regimens, and to identify new pathways to select novel therapeutic agents.

Waiting for further molecular characterization that might lead to identify biologic findings related to aggressive behaviors and treatment resistance, we propose to treat these patients according to the RMS therapeutic strategy, with multi-agents prolonged regimen and local therapy according to patient's age, tumor extension, tumor site, and surgical stage.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data are available on request from the authors.


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