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ONCOLOGY: RESEARCH ARTICLE

Rhabdomyosarcoma with unknown primary tumor site: A report from European pediatric Soft tissue sarcoma Study Group (EpSSG)

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Abstract

Background: Rhabdomyosarcoma (RMS) is an aggressive malignancy, and 20% of children present with metastases at diagnosis. Patients presenting with disseminated disease very occasionally have no clear evidence of a primary tumor mass. As these patients have rarely been investigated, we report on a series of patients with RMS and unknown primary tumor site registered in the Metastatic (MTS) RMS 2008 protocol (October 2008 to December 2016) coordinated by the European pediatric Soft tissue sarcoma Study Group.

Methods: Patients were administered nine cycles of induction chemotherapy, and 48 weeks of maintenance chemotherapy. Surgery and/or radiotherapy were planned after the first assessment of tumor response, and implemented after six cycles of chemotherapy. If feasible, radiotherapy to all sites of metastasis was recommended.

Results: We identified 10 patients with RMS and unknown primary site, most of them adolescents (median age 15.8 years, range: 4.6–20.4). Nine had fusion-positive alveolar RMS. Multiple organ involvement was identified in seven patients, two only had bone marrow disease, and one only had leptomeningeal dissemination. All patients were given chemotherapy, four were irradiated, and none had surgery. Three patients underwent allogeneic bone marrow transplantation. At the time of this analysis, only two patients are alive in complete remission: one had received radiotherapy; and one had a bone marrow transplant.

Conclusions: RMS with unknown primary tumor occurs mainly in adolescents and is typically fusion-positive alveolar. Radiotherapy may be important, but survival is poor and patients should be offered enrollment in investigational trials.

KEYWORDS
bone marrow, rhabdomyosarcoma, unknown origin

Abbreviations: CR, complete response; CT, computed tomography; EFS, event-free survival; EpSSG, European pediatric Soft tissue sarcoma Study Group; IVA, ifosfamide–vincristine–actinomycin D; IVADo, ifosfamide–vincristine–actinomycin D–doxorubicin; MRI, magnetic resonance imaging; MTS, Metastatic; OS, overall survival; PD, progression of disease; PET, positron emission tomography; PR, partial response; RMS, rhabdomyosarcoma; SD, stable disease.

1 | INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive malignancy and the most common soft tissue sarcoma in childhood. It can arise from any part of the body, but the commonest sites are the head–neck region (35%–40%), genito-urinary tract (20%), and limbs and trunk (20%). Two main histological subtypes are recognized: embryonal RMS (75%–80% of cases), and the more aggressive alveolar RMS (20%–30%), characterized by the PAX3/7-FOXO1 translocation, which often presents as metastatic at onset. At diagnosis, approximately 20% of children have distant metastases, the most frequent sites being the lungs, bone marrow, bones, and distant lymph nodes. The survival rate for these patients remains unsatisfactory, and less than 30% of patients are cured.[1,2]

In a few cases, patients present with disseminated disease, but no evidence of a primary tumor mass, sometimes mimicking other cancers such as acute lymphoblastic leukemia. These cases of RMS with unknown primary tumor site have rarely been investigated, and only a few series and case reports are available in the literature.[3–18] A pooled North American–European analysis on metastatic RMS patients included 12 patients with no evident primary tumor site, whose 3-year event-free survival (EFS) was reportedly 8%.[2]

To contribute further information on this rare condition, we report a series of patients with metastatic RMS with unknown primary tumor site registered in the Metastatic (MTS) 2008 protocol coordinated by the European pediatric Soft tissue sarcoma Study Group (EpSSG).

2 | PATIENTS AND METHODS

In accordance with EpSSG recommendations, patients with disseminated disease but no evidence of a primary tumor were classified as metastatic and included in the MTS 2008 study. This prospective international trial was conducted from October 2008 to December 2016 (EudraCT, number 2005-000217-35), and enrolled a total of 270 patients.[19] Inclusion criteria were patients under 21 years old with histologically proven metastatic RMS, no previous treatment, and an interval between diagnostic surgery and start of treatment no longer than 8 weeks. The standard workup included magnetic resonance imaging (MRI) and/or computed tomography (CT) of the primary tumor, chest CT scan, and radionuclide bone scan. 18F-FDG-positron emission tomography (PET)/CT was optional; if performed, the results were used to ascertain tumor extent and establish tumor stage. Staging investigations also included bone marrow aspirates and biopsy. Treatment has been described and included nine cycles of chemotherapy[19]: four cycles of IVADo (ifosfamide, actinomycin-D, doxorubicin on days 1 and 2), followed by five cycles of IVA (same as IVADo, but without any doxorubicin). This was followed by 48 weeks of maintenance chemotherapy with vinorelbine, and daily oral cyclophosphamide.

The tumor response, evaluated after three cycles of IVADo chemotherapy, was evaluated on measurable metastatic lesions (i.e., excluding the bone marrow) classified as complete response (CR) = complete disappearance of all visible disease; partial response (PR) = a tumor volume reduction of more than two-thirds; minor response (MR) = a tumor volume reduction of more than one-third but less than two-thirds. A reduction in volume of less than one-third was recorded as stable disease (SD), while an increase in tumor size or the detection of new lesions was classified as progression of disease (PD).[20]

Treatment of all sites of metastases (with surgery, radiotherapy, or both) had to be implemented after six cycles of chemotherapy. If feasible, radiotherapy to all sites of metastases was recommended.

All participating centers had to obtain written approval from their local authorities and ethics committees, and written informed consent from patients and/or their parents or legal guardians.

A literature search was also conducted in the PubMed biomedical database. The search was performed as of June 2021 using the keywords "rhabdomyosarcoma" and "unknown origin"/"metastatic"/"leukemia." Additional papers derived from the references of the articles retrieved were also analyzed. No restrictions were applied regarding date of publication, but only articles written in English were considered. Our inclusion criteria for the review of patients with metastatic RMS were age between 0 and 18 years and a histologically confirmed diagnosis of RMS.

3 | RESULTS

We identified seven patients with metastatic RMS and no known primary tumor, who accounted for 2.5% of the population eligible for the MTS 2008 study. We identified three more patients registered in the MTS 2008 study, but considered not eligible because of a diagnostic delay (two children) and because the diagnosis was established on cytology alone (one child). We decided to also include these three patients in the present analysis, and the characteristics of all 10 patients are listed in Table 1.

No gender-related difference was noted. Patients were mainly adolescents (median age 15.8 years, range: 4.6–20.4). Symptoms were nonspecific, and a diagnosis of lymphoma had been suspected in three cases (patients 1, 4, and 8) because their symptoms at onset were asthenia, weight loss, and lymphadenopathy. The diagnosis was established from bone marrow aspirates in four patients, peritoneal nodules in two, lymph nodes in two, a bone biopsy in one, and cerebrospinal fluid in one. All patients underwent staging investigations according to the protocol, and eight were also investigated with FDG-PET/CT (Table 1). On reviewing imaging reports, we determined that the extremities were not fully investigated with FDG-PET/CT and/or MRI in three cases (patients 3, 4, and 9 in Table 1). The patient with disseminated leptomeningeal disease was diagnosed as RMS NOS based on cell morphology and immunohistochemistry. All other patients had fusion-positive alveolar RMS, positive for PAX3-FOX1 in eight, and for PAX7-FOX1 in one. Multiple organ involvement was identified in seven patients, while two only had bone marrow disease, and one only had leptomeningeal dissemination. The most often involved organs were bone marrow in six cases, and distant nodes in five. Applying the Oberlin score, which identifies age (<1 or >10 years old), unfavorable primary sites (extremity, other site and unknown primary site), bone

TABLE 1 Patient characteristics

Patient no.	Age (years)/sex	Histology (fusion)	Organs involved	Oberlin score	Therapy	Event	Outcome (months after diagnosis)
1[a]	13.9/M	ARMS (PAX7/FOXO1)	Bone marrow, bone, node, lung, pleura	4	Chemotherapy No surgery, no RT	PD (bone, mediastinum, lung, diaphragm)	DOD (12)
2[a]	15.7/M	ARMS (PAX3/FOXO1)	Bone marrow	3	Chemotherapy No surgery, no RT ABMT	New MTS (CNS)	DOD (10)
3[a]	16.5/F	ARMS (PAX3/FOXO1)	Pleura, peritoneum	2	Chemotherapy No surgery, no RT ABMT	No	Alive in CR (94)
4	12.3/F	ARMS (PAX3/FOXO1)	Bone marrow, node, diaphragm, pericardiac	4	Chemotherapy (1 cycle) No surgery, no RT	No	Death due to cardiac arrest (0.5)
5[a]	20/4F	ARMS PAX3/FOXO1	Node, peritoneum	2	Chemotherapy RT No surgery	PD (node)	DOD (17)
6[a]	4.6/M	RMS NOS (MD)	Leptomeningeal dissemination	1	Chemotherapy RT, No surgery	No	Alive in CR (101)
7[a]	16.7/M	ARMS (PAX3/FOXO1)	Bone marrow	3	Chemotherapy No surgery, no RT ABMT (post PD)	PD (bone marrow)	Death due to toxicity (6)
8[a]	16/F	ARMS (PAX3/FOXO1)	Bone marrow, bone	3	Chemotherapy RT No surgery	No	DOD (18)
9	13/F	ARMS (PAX3/FOXO1)	Bone marrow, node	3	Chemotherapy RT No surgery	New MTS (lung)	DOD (24)
10[a]	6/F	ARMS (PAX3/FOXO1)	Bone, node	2	Chemotherapy RT No surgery	Relapse after CR (bone and node)	DOD (40)

Abbreviations: ABMT, allogeneic bone marrow transplantation; ARMS, alveolar rhabdomyosarcoma; CR, complete remission: DOD, died of disease; IVA, ifosfamide, vincristine, actinomycin-D; IVAdo, ifosfamide, vincristine, actinomycin-D, doxorubicin; MTS, metastasis; PD, progression of disease; RT, radiotherapy.

[a]Patients investigated with FGD PET/CT.

or bone marrow involvement, and more than three metastatic sites as correlating with a negative prognosis,[2] our series included one patient with one, three patients with two, four patients with three, and two patients with four of these risk factors.

All patients received chemotherapy according to the protocol. After the first three cycles, three patients were in CR and three were in PR, while one patient had SD and one had PD. One more patient with bone marrow as the only involved organ (patient 2 in Table 1) was in CR, as demonstrated by bone marrow aspiration and biopsy. One patient with intracardiac tumor died of cardiac arrest before being assessed for tumor response. Radiotherapy was administered to five patients (in doses ranging from 41.4 to 50.4 Gy). In particular, the patient with leptomeningeal dissemination received craniospinal irradiation, one patient with peritoneal dissemination received whole abdominal irradiation, two children had radiotherapy to bone lesions, and one patient received lymph node irradiation. No patient had surgery. Three patients received an allogeneic bone marrow transplant at the local center's discretion (after bone marrow progression in one case).

At the time of this analysis, two patients are alive in CR, 94 and 101 months after their diagnosis. Of the eight who died, four had tumor progression, two developed new metastases (one during treatment), one had a cardiac arrest after the first cycle of chemotherapy, and one died of transplant-related toxicity (not further specified). One of the two patients still alive received radiotherapy.

4 | DISCUSSION

This report describes a series of patients with no evidence of a primary lesion, and therefore considered as having RMS with unknown primary site. This is a rare condition and represents a diagnostic and therapeutic challenge.

The diagnostic difficulties clearly emerge from our study: despite the usual diagnostic workup (including FDG-PET/CT in eight cases), clinicians were unable to identify a clear primary lesion in these 10 patients registered in the EpSSG MTS 2008 protocol. We know that small tumor lesions localized in the extremities may give widespread

TABLE 2 Reported cases of rhabdomyosarcoma with no identifiable primary soft tissue mass in pediatric age

No. (ref)	Age (years)/sex	Histology	Organs involved	Therapy	Events	Outcome (follow-up in months)
1 [9]	13/F	ERMS	Bone	Chemotherapy: VAC Surgery and RT	MTS	MD
2 [10]	18/M	ARMS	Bone, distant nodes, pleura	MD	MD	MD
3 [11]	18/M	RMS	Bone, bone marrow	Chemotherapy: VAC No surgery, no RT	PD	DOD (8)
4 [12]	MD	ARMS	Bone, distant node	MD	MD	Alive (5)
5 [12]	MD	ARMS	Bone, distant node, pleura, peritoneum, bone marrow	MD	MD	Alive (5)
6 [12]	MD	RMS	Bone, bone marrow	MD	MD	Alive (6)
7 [12]	MD	RMS	Bone, bone marrow	MD	MD	DOD (4)
8 [13]	19/M	RMS	Bone, distant node	Chemotherapy: VAdC No surgery, no RT	NO	MD
9 [14]	8/M	ERMS	Bone, bone marrow	Chemotherapy: CEVAIE	PD	AWD (12)
10 [15]	12/F	ARMS	Bone	Chemotherapy: MD RT	MD	DOD (3)
11 [15]	15/F	ARMS	Bone	Chemotherapy: MD	MD	DOD (12)
12 [15]	15/F	ARMS	Bone	Chemotherapy: MD RT	MD	AWD (14)
13 [16]	18/F	RMS	Bone marrow	Chemotherapy: VAC + VAdC	RD	DOD (9)
14 [17]	15/M	ARMS	Bone marrow, bone	MD	MD	MD
15 [18]	12/M	ARMS	Bone marrow	MD	NO	DOD (3)
16 [19]	14/M	ARMS	Distant node, bone marrow	Chemotherapy: etoposide, cyclophosphamide, pirarubicin, cisplatin, vincristine, ABMT	NO	Died due to toxicity (8)
17 [20]	16/M	ARMS	Bone marrow	Chemotherapy: etoposide, ifosfamide, vincristine, adriamycin. Cyclophosphamide	RD	DOD (8)
18 [21]	14/M	ERMS	Bone marrow, distant node, pleura, peritoneum	Chemotherapy: CEVAIE	MTS	DOD (9)
19 [22]	4/F	RMS	Bone	Chemotherapy: VAC + etoposide	PD	DOD (MD)
20 [23]	17/M	ARMS	Bone	Chemotherapy: CEVAIE No RT	PD	DOD (7)
21 [23]	9/M	ARMS	Bone	Chemotherapy: CEVAIE No RT	MTS	DOD (30)
22 [24]	18/M	ARMS	Bone, bone marrow, distant node	MD	MD	MD

Abbreviations: ABMT, allogeneic bone marrow transplantation; ARMS, alveolar rhabdomyosarcoma; AWD, alive with disease; CEVAIE, carboplatin, epirubicin, actinomycin-D, etoposide, ifosfamide; DOD, died of disease; ERMS, embryonal rhabdomyosarcoma; MD, missing data; PD, progression of disease; RD, relapse of disease; RMS, rhabdomyosarcoma; RT, radiotherapy; VAC, vincristine, actinomycin-D, cyclophosphamide; VAdC, vincristine, adriamycin, cyclophosphamide.

dissemination,[21] unfortunately three patients in our series were not fully investigated in this sense and we cannot exclude as they had an unrecognized extremity primary tumor. Careful clinical examination and whole-body MRI or FDG-PET-CT/MRI scanning is suggested for all patients with disseminated RMS if the primary site is not immediately apparent.[20] Another possible limitation of our study concerns the inclusion of a child with disseminated leptomeningeal disease and only a cytological diagnosis: we decided to include this patient in our series because he was considered and treated like a case of metastatic RMS.

The frequent involvement of the bone marrow (it was the only organ involved in two cases) may support the hypothesis that it could be the primary tumor site, rather than a site of dissemination. We cannot prove a primary bone or bone marrow origin, but recent studies found that RMS can originate from an aberrant development of non-myogenic cells.[22] This would justify the initiation of RMS at sites like the bone marrow and bone.

The MTS 2008 results have been recently published, and a 3-year EFS 35.5% and overall survival (OS) 49.3% have been reported for the whole population. Patients with an Oberlin score >3 presented a worst outcome: 3-year EFS 12.5% and OS 26.0%.[19] It is possible that patients with unknown primary have a poor prognosis because they tend to have a higher Oberlin score (six patients with score >3 in our series). However, we know that the treatment of patients with disseminated disease but unknown primary tumor presents a series of obstacles. Local control measures are fundamental in the treatment of RMS, but the absence of a primary lesion often precludes the use of local surgery or radiotherapy, and it is difficult to administer radiotherapy as the disease is frequently widely disseminated and when bone marrow is involved. This is an important aspect as our recent experience suggests that radiation is associated with improved survival in metastatic RMS.[23] Chemotherapy was the only treatment modality used in most of our patients, and was unfortunately not enough: only two patients in our series are still alive. The predictably poor prognosis may explain why clinicians chose to perform an allogeneic bone marrow transplant during first-line treatment in three patients, although there is no clear evidence to indicate that it is effective in RMS. A very recent study found no improvement in patients with metastatic alveolar RMS when treated with allogeneic bone marrow transplant.[24] As only one of transplanted patients is still alive, so we can draw no firm conclusions regarding potential efficacy of this procedure, which carries a small but significant risk of mortality.

The poor prognosis of this group of patients is confirmed by a review of the medical literature. We found 16 publications (from 1976 to the present) describing 22 cases of children with RMS and an unknown primary tumor site.[3–18] The characteristics of these patients are summarized in Table 2. As in our series, this condition seemed to be more typical of the fusion-positive alveolar subtype of RMS, and occurred mainly in adolescents. The most frequently involved sites were the bone marrow, bone, and distant lymph nodes. A lymphoproliferative disease was often suspected, and the diagnosis was made on analyzing the bone marrow.

All patients were treated with chemotherapy, while radiotherapy and surgery were performed in a few cases.

Only three patients out of 17 with outcome data were reportedly alive with no sign of disease, but the follow-up was short.

In conclusion, metastatic RMS with no clear evidence of a primary site is a rare condition, more likely to affect adolescents and to involve the fusion-positive alveolar histotype. Current treatments are rarely able to cure these patients, who should be included in investigational trials along with other very high-risk, metastatic patient groups.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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