Introduction

Ectomesenchymoma is a rare mesenchymal malignancy occurring mainly in the pediatric population. The hallmark diagnostic features are a combination of sarcoma, usually rhabdomyosarcoma with admixed ganglion cells. The lesion arises either in soft tissues or the cranial cavity and outcomes vary considerably. Current knowledge about the genetics and biology of ectomesenchymoma are extremely limited with a total of four published karyotypes, showing overlaps only in trisomies 2, 8 and 11. Here we describe a case with genetic findings that, in conjunction with pre-existing observations, offers some additional insights into the genetic aberrations of ectomesenchymoma.

Case History

Our patient presented at age 6 months with a mass protruding from her vagina. Biopsy was taken and showed classic histology of botryoid embryonal rhabdomyosarcoma [see pathology below]. Imaging revealed a vaginal mass and separate para-aortic lesion together with enlarged bilateral iliac nodes. Following 5 months of RMS-directed chemotherapy (ifosfamide, vincristine, actinomycin, doxorubicin), as per the EpSSG RMS 2005 protocol, she had a macroscopic complete resection of the pelvic/vaginal mass, including a para-aortic abdominal lesion. Histology showed viable rhabdomyosarcoma tumor cells in at least 50% of the resected tumor. Scattered ganglion-like cells were also identified. Evolution into ectomesenchymoma was diagnosed and chemotherapy was intensified (irinotecan, topotecan, vincristine and carboplatin in combination) as a result of this poor response, but she developed progressive abdomino-pelvic tumor requiring further biopsy four months later. Histology at this time showed Schwannian stroma containing scattered ganglion cells — morphologically a neuroblastic tumor. Therapy was altered to include cisplatin and etoposide. The abdomino-pelvic tumor progressed on treatment and anaplastic features were evident on a biopsy two weeks later (nine months post-initial diagnosis). Further progression was confirmed by fine-needle aspiration biopsy of an umbilical nodule at 12 months post-initial diagnosis and subsequent management was with palliative intent until the patient’s demise three months later.

Pathology and Genetics

Initial biopsy was that of classic embryonal rhabdomyosarcoma with no trace of ganglionic differentiation. The growth pattern was botryoid with a well-developed cambium layer present. Immunostaining was strongly positive for desmin and in a subset of cells for myogenin and MyoD1, as expected in ERMS. The post-treatment resection specimen was multi-lobular with a whorled, tan cut surface appearance with focal fleshy brown areas. Microscopy showed some evidence of cyto-differentiation compared with the pre-treatment biopsy, and only minimal necrosis. The tumor contained scattered ganglion-like cells. Nodules of primitive, undifferentiated spindle cells were present at the peripheries of the mass. These primitive cells showed strong reactivity for myogenin and MyoD1. Ki-67 stained a large fraction of these nuclei also. Calretinin stained large, ganglion-like cells. Biopsy from the relapse at the base of bladder
four months later showed morphological neuroblastic tumor containing ganglion cells, neuropil
and a prominent Schwannian stromal component, effectively ganglioneuromatous tissue. The
cells showed strong reactivity for CD56, however ganglion-like cells also stained strongly for
both calretinin and desmin, while there was no reactivity for myogenin or MyoD1. Two weeks
later, biopsy of residual tumor at the base of bladder showed large, anaplastic cells in a
background population of small, primitive cells. The small primitive cells stained diffusely with
CD56, while the larger anaplastic cells were positive for CD56 and a sub-population stained
strongly for desmin. The features on these cores were of anaplastic embryonal
rhabdomyosarcoma in the anatomic region of prior apparent ‘pure’ neuroblastic morphology.

**Discussion**

Ectomesenchymoma is a rare malignancy of soft tissues comprising a combination of malignant
mesenchyme, most commonly rhabdomyosarcoma, with admixed neural elements, occasionally
with additional heterologous mesenchymal elements present also, and occurring predominantly
in the pediatric population [2;3]. Ectomesenchymoma is thought to arise from neural crest cells,
which might serve to explain the divergent differentiation. Per the WHO classification,
etomesenchymoma belongs to the rhabdomyosarcoma group and this categorization is
corroborated by genetic profiling study suggesting that ectomesenchymoma shows
rhabdomyosarcomatous differentiation [4] although an isolated intracranial case was reported
to segregate with MPNST rather than a variety of other pediatric solid malignancies including
RMS [5]. Ectomesenchymoma may occur as an intracranial primary or in the soft tissues,
peripheral and deep-seated alike. A review of 39 cases showed preponderant presentation
during the first decade of life [81%] with a 17:13 female: male ratio. 82% had
rhabdomyosarcomatous elements while 29% contained ganglion cells [6]. While
etomesenchymoma may be a primary diagnosis, cases also exist where initial diagnosis was of
rhabdomyosarcoma with either a metastasis post-therapy [7] or relapse post-therapy [8]
declaring itself as ectomesenchymoma. In the former setting, electron microscopic examination
showed not only clear-cut myogenic and ganglionic differentiation, but also a population with
overlapping fine structural phenotype in addition to overlapping immunophenotype. While we
did not conduct electron microscopic examination of our case, we did find overlapping neural
and muscle marker reactivity in the post-treatment resection specimen and at any rate, ganglion
cells are not a morphological feature usually identified in post-treatment rhabdomyosarcoma.

Biologically, this tumor behaved very aggressively compared with embryonal
rhabdomyosarcoma, insofar as there were early and multiple relapses, treatment-resistance to
standard and intensified rhabdomyosarcoma protocols, and then rapid progression to death.
Apart from the case reported by Floris to show trisomy 2, 11 and 20 in addition to focal gains on
chromosome 6 [6p21; 6p11] [4], there are but three reports in the literature with cytogenetic
data [see table below]. One of these showed polyploidy of chromosomes 2, 8 and 11 [9] while
another was a case arising within kidney and consisting of a spindle cell sarcoma containing heterologous chondroid material and ganglion cells. The case showed trisomy 2, 8, 9, 10, 11, 20 and gain of 6p24 in addition to t(12;15)(p12.3;q24.1) [1]. Despite the provocative finding of t(12;15) in a renal tumor of a toddler, the diagnosis of cellular congenital mesoblastic nephroma was ruled out based on morphology. No further characterization of the transcript involved was reported in that case. The current case showed t(1;12)(p32;p13) and with FISH using a commercial ETV6 probe, we were able to ascertain that ETV6 was not rearranged. Insufficient material was available for further characterization of the transcript resulting from this chromosomal translocation, but apparently the precise breakpoint on chromosome 12 is different from that in CCMN/CFS. Our case is a second ectomesenchymoma showing rearrangement of 12p13. Rearrangement of 12p13 in the context of t(12;15)(p13;q24) is known to be cryptic on karyotypic analysis, and if balanced, might be missed by other assays such as aCGH. A pattern however emerges whereby ectomesenchymomas genetically worked up to-date may share the features of trisomies, also seen in a variety of other pediatric malignancies, and potentially gains of chromosome 6p additionally. Outcomes appear to vary considerably in these patients, with about half now going on to long-term survival. A more in-depth understanding of the biology of these tumors should assist in prognostication.
Karyotype from this case: 46XXder(1)t(1;12)(p32;p13)inv(1)(p13q25), del(5)(q13q22), der(12)t(1;12)(p32;p13)[9]/46,XX[3] from the cultured tumor cells. Rearranged chromosomes 1 and 12 are indicated by red arrows.
References:


Table – karyotypic data from the literature for ectomesenchymoma:

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Spindle cell renal tumor arising in a toddler. [Ref 1]</th>
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<tbody>
<tr>
<td>53,XY,+2,add(6)(p24),+8,+8,+9,+10,+11,t(12;15)(p12;q24),+20</td>
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</tbody>
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<tr>
<th>Case 2</th>
<th>Scrotal mass in an 8 months old boy. [Ref 4]</th>
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<tbody>
<tr>
<td>49,XY,+2,-6,+11,+20,+mar[chromosome 6 material by FISH].</td>
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<tr>
<th>Case 3</th>
<th>Malignant ectomesenchymoma arising intracranially in a 4-year old girl. [Ref 5]</th>
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</thead>
<tbody>
<tr>
<td>84-87,XXX,-1,der(2)t(1;2)(q12;q14.1),-4,-5,-5,der(5)t(5;?;5)(p15;?;q13)x2,</td>
<td></td>
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<tr>
<td>-9,-9,del(11)(q22)x2,-17,-19,-21,der(21)t(17;21)(q21;q22),-22,-22,</td>
<td></td>
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<tr>
<td>+r,+mar1,+mar2,+mar3[cp10]</td>
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<th>Case 4</th>
<th>Perineal mass in a five month old baby. [Ref 9]</th>
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<tr>
<td>49,XY,+8,+8,+11/49,XY,+2,+11</td>
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