# To Treat or Not to Treat? Facing Spontaneous Remission of a Neonatal Malignant Mesenchymal Spindle-Cell Neoplasia

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**Abstract**

We report a case of malignant mesenchymal spindle-cell neoplasia of the skull, diagnosed in a female newborn at 13 days of age by biopsy and subtotal resection. Considering the good clinical condition, the age, tumor histology and the risks associated with surgery and chemotherapy, we proposed a "wait and see" approach with a close radiologic monitoring of the tumor lesion. Surprisingly the tumor showed spontaneous regression both at MRI and ultrasound evaluations. To date, after 12 months of observation, MRI showed sustained remission: the infant recovered from surgery and maintains good clinical condition while follow-up is ongoing.

**TITLE** :

To Treat or Not to Treat? Facing Spontaneous Remission of a Neonatal Malignant Mesenchymal Spindle-Cell Neoplasia.

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**LIST OF ABBREVIATIONS:**

| | |
|---|---|
| **MRI** | **Magnetic Resonance Imaging** |
| **CT** | **Computer Tomography** |
| **PCR** | **Polymerase Chain Reaction** |
| **FISH** | **Fluorescent In Situ Hybridization** |
| **FNCLCC** | **FédérationNationaledes Centres de LutteContre Le Cancer** |
| **PNET** | **Primary Neuroectodermal Tumors** |
| **SIOP** | **Society of Pediatric Oncology** |
| **RMS** | **Rhabdomyosarcoma** |

**ABSTRACT:**

We report a case of malignant mesenchymal spindle-cell neoplasia of the skull, diagnosed in a female newborn at 13 days of age by biopsy and subtotal resection.

Considering the good clinical condition, the age, tumor histology and the risks associated with surgery and chemotherapy, we proposed a "wait and see" approach with a close radiologic monitoring of the tumor lesion. Surprisingly the tumor showed spontaneous regression both MRI and ultrasound evaluations.

To date, after 12 months of observation, MRI showed sustained remission: the infant recovered from surgery and maintains good clinical condition while follow-up is ongoing.

**MAIN TEXT:**

Case Description -

A full term female neonate born by vaginal delivery after regular gestation showed a rapidly growing retroauricolar swelling after 5 days of life, requiring hospitalization at 9 days of life. The newborn was febrile with elevated phlogosis indexes, thus intravenous empiric antibiotic therapy was started. The MRI and CT scan showed an expansive lesion of the right petrous bone of unknown origin (Fig. 1). The images were compared to those obtained from the fetal MRI performed during gestation due to periventricular white matter increased echogenicity, showing no in utero malformation.

At 13 days of life, a biopsy with subtotal resection of the lesion was performed due to volume increase of the neoplasm, especially with disruption of temporal bone and with cervical-lateral extension limiting head and neck mobility. The surgeon described an "encapsulated lesion that reveals siero-hematic content". Intraoperative pathology showed spindle-cell malignant neoplasia.

Initial molecular analysis (PCR and FISH) resulted negative for ETV6-NTRK3 translocation and *USP6* gene rearrangements ruling out the suspect of infantile fibrosarcoma and cranial fasciitis respectively [1; 2]. Moreover tumor tissue was analyzed by next generation sequencing to further identify strong fusions

and oncogenetic isoforms of the following genes: *ALK CAMTA1, CCNB3, CIC, EPC1, EWSR1, FOXO1, FUS, GLI1, HMGA2, JAZF1, MEAF6, MKL2, NCOA2, NTRK3, PDGFB, PLAG1, ROS1, SS18, STAT6, TAF15, TCF12, TFE3, TFG, USP6, YWHAE* . The final histologic diagnosis was "malignant mesenchymal spindle-cell neoplasia, grade 2 (according to FNCLCC classification [3;4])"

A multidisciplinary evaluation was carried out: looking at lack of indication to proceed with chemotherapy regimens in this histology, the strong therapy-related toxicity reported in the newborn and the potentially mutilating radical surgery, we proposed a "wait and see" approach with a rigorous radiologic follow-up consisting of ultrasound every 2 weeks and monthly MRI.

The evaluation at 2 months of life showed a significant volumetric reduction (Figs. 2A and 2B). The lesion appeared confined in the right petrous bone without any vascular involvement.

Since the first MRI showed spontaneous regression and considering the good clinical conditions of the patient, we decided to further continue the radiologic follow-up without other interventions.

MRI at 4 and 7 months of life confirmed the continuous spontaneous regression of the lesion (Figs. 2C and 2F).

Next MRI is scheduled in two months; to date, the patient maintains good clinical conditions and automatic acoustic evaluation shows no signs of hearing damage so far.

Discussion -

Rapidly growing neonatal masses represent a great therapeutic challenge for the physician: since they remain a rare occurrence, data about treatments and protocols are scarce. Treatment decisions in the infantile population must be evaluated carefully, especially in the first months of life, since surgery sequelae, radiotherapy and chemotherapy toxicity pose great concerns [5-6].

Neonatal tumors encompass a heterogeneous group of diseases, ranging from benign lesions (such as lymphatic malformations) to malignant neoplasms (such as soft tissue sarcomas). More than 75% of soft tissue tumors diagnosed in the first year of life show a benign pathology, 10% are borderline lesions, and only 15% show malignant characteristics [7]. Malignant soft tissue sarcomas of the infancy are rare diseases with an estimated incidence of 1.6/100.000 children $<$ 1 year of age [8].

Although it might be difficult to obtain a precise characterization of these tumors, it is important to identify soft tissue primary neuroectodermal tumors (PNETs), as the prognosis of this particular subset of non-Rhabdomyosarcoma (RMS) neoplasm is poor and may require aggressive treatment [9].

Previous reports from the Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor Committee suggest that RMS is the most frequent histology, with undifferentiated spindle-cell sarcomas representing a small group of non-RMS histologic type [6]. The term "undifferentiated sarcomas" highlights the lack of specific immunohistochemical and molecular features, and it has been used extensively to identify a wide range of tumors with variable biology and clinical behavior [10; 11]. Alaggio et al. suggested that undifferentiated sarcomas might developed as a result of an arrested maturation of the mesenchymal fibroblastic stem cell in its maturative path towards fibroblast-myofibroblast-pericyte [11] but specific molecular diagnostic markers are lacking and therapeutic approaches might vary.

A recent case series highlights the favourable clinical course of congenital undifferentiated sarcomas treated with surgery, chemotherapy or a combination of the two, with four patients out of five alive without recurrence after 1-11 years of follow-up [9], but lacked information about molecular analysis. However, spontaneous remission of undifferentiated spindle-cell sarcomas is reported in past case series [6] but since the number of patients is limited, choosing the wait-and-see approach over the treatment could be a very difficult decision. In our case molecular cytogenetic analysis and NGS studies were particularly helpful to rule out most of the more aggressive tumor histologies, making possible a wait and see approach.

Age at diagnosis has been considered as a potential favourable prognostic factor for STS: past reports from

the German Soft Tissue Sarcoma Study Group showed that whilst children diagnosed with RMS in the first year of life have a poor prognosis, other histologies show a more favorable behavior in infants than in older children, with an overall survival reported as high as 100% for congenital fibrosarcoma [12]. However, for non-RMS mesenchymal tumors, Orbach et al. reported no statistically significant differences of the overall prognosis between infants and older children [6].

Another factor investigated in the literature that might correlate with the outcome is primary anatomic site of the infantile undifferentiated sarcomas: in their series, Alaggio et al. suggested that truncal location correlates with aggressive clinical behaviour, whilst the subset with fibrosarcoma-like characteristics that showed a favourable outcome developed on the extremities [11], with the only patient diagnosed with undifferentiated sarcoma with less than one year at diagnosis emerging from the extremities.

After almost one year of follow-up, our patient still maintains clinical remission: even without a biological mechanism explaining the tumor regression, we think it is important to share our experience with this rare congenital neoplasm which confirms the need to keep in mind the principle of "primum non nocere".

**CONFLICT OF INTEREST STATEMENT:**

The authors declare no conflict of interest.

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**LEGENDS**

Figure 1: CT scan images on axial (A) and coronal (B) planes. Partially cystic, expansive lesion infiltrates and erodes the petrous bone, extending with its more solid component, above the mastoid region, inferiorly along the upper portion of the latero-cervical region (A and B). The lesion extends intracranially, budging within the adjacent portion of middle and posterior fossa. (C) Axial 3D T2 weighted-imaging better highlights the inhomogeneous cystic content and the infiltration of the posterior part of the bony labyrinth. (D) CT scan axial imaging showing the removal of the mastoid part of the lesion, with air within the surgical cavity (arrowhead).

Figure 2. Serial MR axial fat-saturated images T2 images at the mid-level of the bony labyrinth (upper row) and slightly inferiorly (lower row), performed 1 (A, B), 4 (C, D) and 7 (E, F) months after surgery. The images clearly shows the significant volumetric reduction of the lesion (arrowheads) with ossification of the petrous bone and the inner ear bony structure (dotted line in A and C).