Complete Remission of Pediatric Rhabdomyosarcoma with Metronomic Chemotherapy

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History:

- Received: March 19, 2020
- Accepted: June 25, 2020
- Published: Sept 1, 2020

DOI: https://doi.org/10.31838/ejmcm.07.01.16

ABSTRACT

Rhabdomyosarcoma occurs commonly in the head and neck, seen mostly in the parameningeal region. We report, a 5-year-old boy presented with a history of painless progressive protrusion of the left eye (LE) and progressive headache and strabismus suddenly with the impression of rhabdomyosarcoma of mastoid protruded to orbit, who resistant to conventional and salvage chemotherapy. Finally, he was cured by metronomic chemotherapy (Vinorelbin and Cyclophosphamide) completely.

Keywords: Complete remission, Pediatric rhabdomyosarcoma, metronomic chemotherapy.

INTRODUCTION

Rhabdomyosarcoma develops in the head and neck, seen mostly in the parameningeal area. The ear and mastoid bone are uncommon area of disease. Rhabdomyosarcoma of the parameningeal area has an unfavorable prognosis.

Mimicking features of acute otitis media is one of the clinical features of rhabdomyosarcoma in the mastoid bone and ear. This similarity can lead to a retarded diagnosis of ear and temporal bone rhabdomyosarcoma. Cranial nerve palsy and intracranial extension are features of advanced disease.

The role of inexpensive treatment modalities such as metronomic chemotherapy, especially in the developing countries, is increasingly being recognized and their practices are sometimes associated with favorable results (1).

CASE PRESENTATION

A 5-year-old boy presented with a history of painless progressive protrusion of the left eye (LE), headache, and strabismus, suddenly. In addition, he had severe lower limb pain and frequent vomiting. He had a history of upper respiratory infection last week before ocular signs. He had not has a history of trauma.

He was admitted to the children's hospital. Primary brain MRI was normal immediately after the initial presentation. He was treated by Prednisolone 2 mg/kg/d. There was not any history of nose bleeding and nasal grip. His visual examination was normal, but he had cranial nerves palsy in VII and VIII nerves. The light pupil reflex was intact.

He was treated by Ceftriaxone followed by Co-Amoxiclave for otitis media. After 2 weeks of treatment and sustained ear pain, he was done under mastoid and temporal MRI. The MRI was presented an orbital heterogeneous mass was originated from the apical area of the mastoid. In addition, second brain MRI showed a mass lesion with a hyper-signal component that is protruding in the cerebellopontine angle.

The left mastoidectomy was performed and mass lesion resected for biopsy. A final diagnosis of orbital mass after immunohistochemistry (immunohistochemical staining showed that myogenin and Desmin were positive, and negative for the epithelial markers were)

Laboratory tests showed an erythrocyte sedimentation rate of 60 mm/h, white blood cells 6.2 × 10 9, neutrophils 54%, lymphocytes 25%, monocyte 3% and eosinophils 2%, presence of anisocytosis, hemochromatosis, and sufficient platelets. After surgery pain developed in the left ear (LE), and the eye had severe chemosis and redness. The visual acuity LE decreased severely. The patient had left cervical area lymphadenopathy, without any masses.

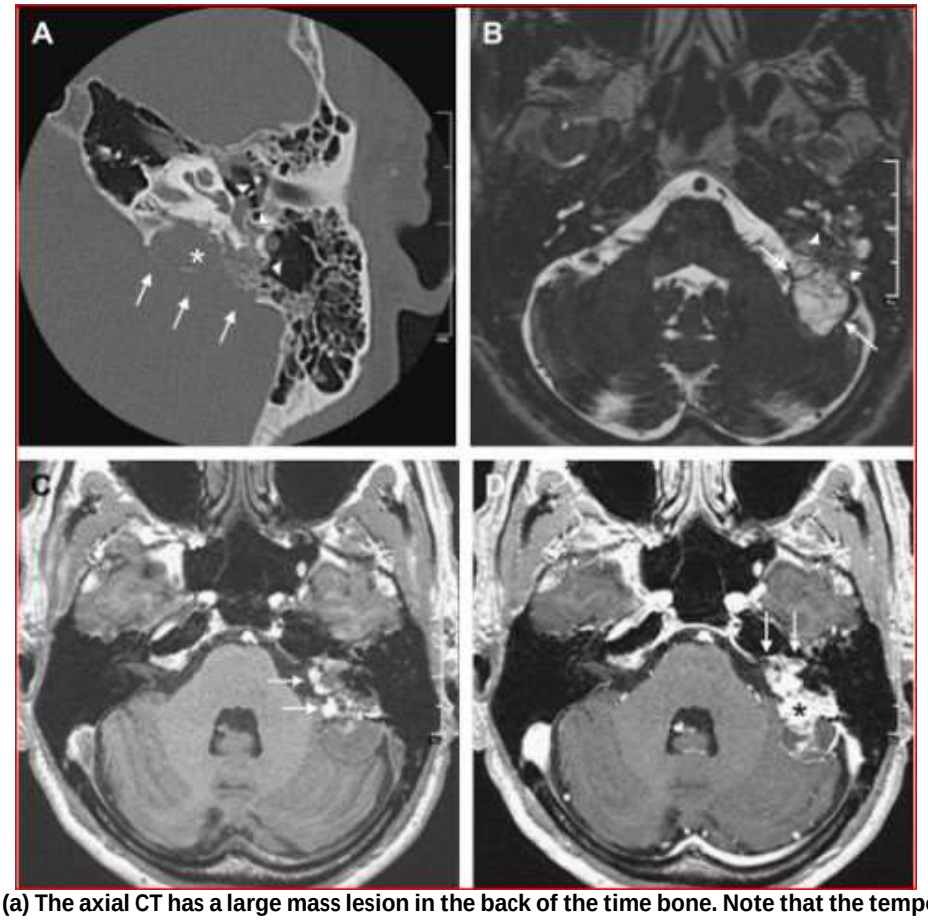

Figure 1: (a) The axial CT has a large mass lesion in the back of the time bone. Note that the temporal bone (arrows) has an irregular disorder. The pyramidal eminence invasion and the center ear (arrowheads) cause paralysis of the face. (b) Axial imagery of T2-weighted MR by membrane labyrinth. Large hypo-signal mass lesions characterize the rear side of the temporal bone (arrowhead). The cerebellopontine angle (arrows) forms part of the mass lesion with a hypesignal component. (c) The mass lasion in the cerebellopontine angle with typical peripheral hypersignal (arrows) is seen by T1-weighted left time-bone MR imagery. (d) The T1-weighted MR of axial postgadolinium exhibits a strong reinforcement on the backside of the left temporal bone of the mass lesion.

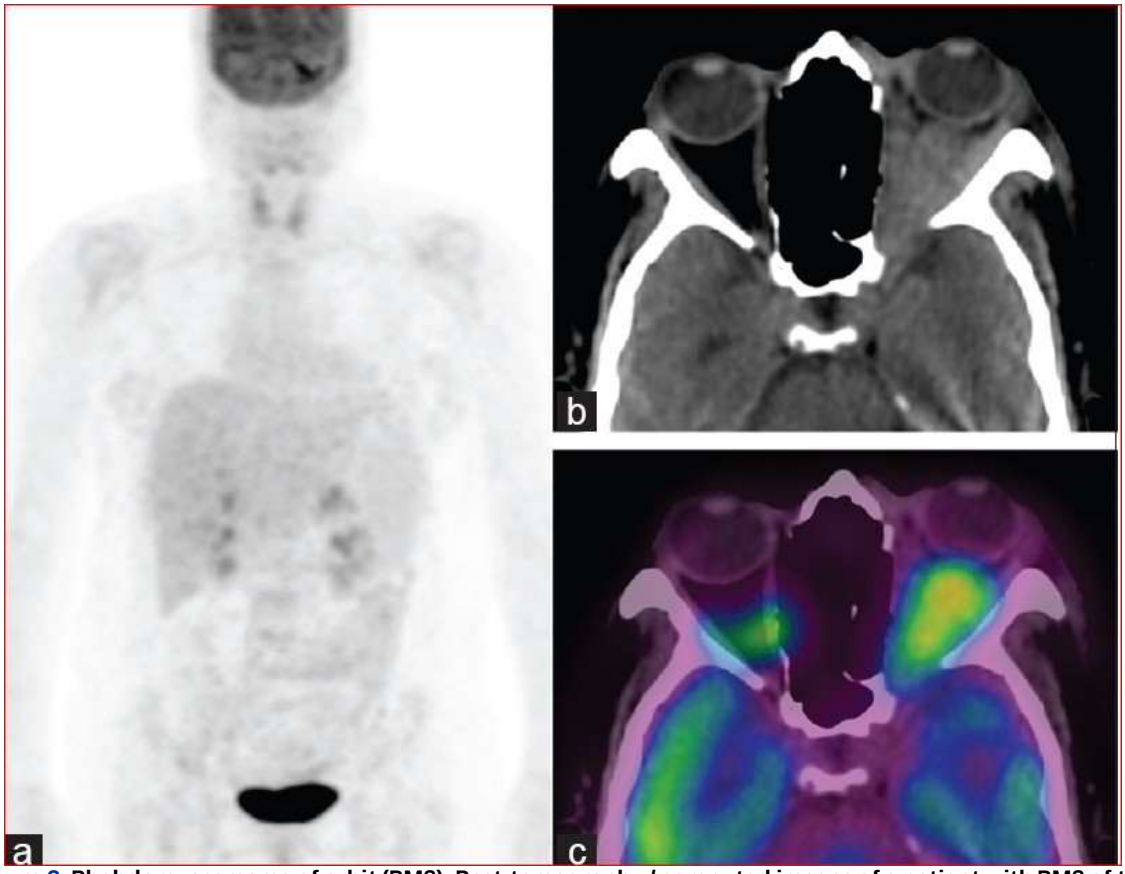

Figure 2: Rhabdomyosarcoma of orbit (RMS): Post-tomography / computed images of a patient with RMS of the left orbit fluorodeoxyglucose. Maximum intensity projection image (a) shows no systemic tumoral involvement. (b and c)

He has been referred to the department of pediatric oncology and the proposed chemotherapy treatment. He was treated by conventional chemotherapy including Vincristine, Ifosfamide (1,800 g/m2/day), Etoposide (100 mg/m2/day) and Mesna (1,080 mg/m2/day) for 5 days (6 courses) with Vincristine 1.5 mg/m2 weekly, and Dexamethasone radiotherapy, but unfortunately, he did respond to treatment. Therefore, he was treated by salvage protocol include:

1- Vincristine 1mg IV d1, Melphalan 6mg/m^2/d p.o (2 courses); and due to no response,
2- Topotecan and Cyclophosphamide 0.75 and 250 mg/m^2/day × 5 days q3-4 weeks (5 courses), respectively.

While the tumor was treated, its dimension began to increase, including Vinorelbine and oral cyclophosphamide, which were treated using a metronomic chemotherapy regimen. Vinorelbine administrated at 25 mg/m2 per week in the first 12 weeks intravenously and Cyclophosphamide 50 mg/m2 orally once daily continuously, biweekly afterward was used with low dose at 50 mg/m2/day orally. After one year during follow up visits, the tumor disappeared. The whole-body PET scan was negative.

DISCUSSION

Rhabdomyosarcomas may come from different locations, mainly in orbits, skull base, cavity and nasopharynx or tympanic areas of the head and neck. In the head and neck regions, the tympanic area and mastoid bone in children were about 30 to 40 percent unusual. Chao et al. (2) reported three patients with temporary bone involvement. In 1966, Potter reported rhabdomyosarcoma on the right external auditory canal in a 3-year-old child with bilateral otitis medicines and polypoid mass. The larynx's embryonic rhabdomyosarcoma in a 33-year-old male reported by Kukwa et al. in 2011 (3).

In a study conducted in 2007, Sbeity S identified 39 rhabdomyosarcoma patients in the head and the throat area, of whom only 6 children were rhabdomyosarcomas in the temporal bone. At diagnosis, the average age was 4.15 years. The most prevalent clinical diagnosis was chronic otitis media (4).

Vegari reported that a three-year-old girl was referred to the clinic because of her right ear's serosanguine discharge. It was diagnosed as embryonic rhabdomyosarcoma after paraclinical and pathological evaluations. This report showed that rhabdomyosarcoma should be taken as a differential diagnosis in mastoiditis, particularly in young children (5).

Treatment options such as Proton beam radiation, IGF-1R inhibitors, stereotactic body radiation therapy (SBRT), cixutumumab and ganitumab mTOR protein, temsirolimus and everolimus, drugs that target the cell's hedgehog pathway, such as sonidegib have expensive cost and

developed facilities which aren't exist or limitation in Iran (6).

There is also a major therapeutic scope for developments in patients in countries with low and middle-income refractory diseases. metronomic chemotherapy (7).

Metronomic chemotherapy Treatment is performed on a continuous schedule of low doses of anticancer medicines (each day or week) (8). This method was originally designed to overcome drug resistance by shifting the therapeutic objective from tumor cells to endothelial tumor cells, using a non-toxic dose without longer rest periods. The immune system (immunomodulation) and the tumor cells also suffer from anti-tumor effects. Host anti-tumor immunity is the goal of immunotherapy (9).

Its main mechanisms include preventing tumor angiogenesis and modulation of the immune system of hosts, which directly affect the tumor cells, progenitors, and neighboring current cells. The main advantages over conventional therapies are its better toxicity profile, reduced costs and easier use. There is increasing evidence of metronomic chemotherapy for individual medicine. Unfit Elderly and Palliative Care MC Management is also developed (10).

The number of clinical trials of metronomic chemotherapy is very limited in children compared to adult patients.

In children with medulloblastoma, Sterba et al. reported positive results to metronomic temozolomide with radiation therapy.

This time, different metronomic chemotherapy regimens for varying patients and different childhood cancers have been used in pediatric malignancies (11).

Metronomic is already used in countries with low and medium income (LMICs) and represents a potential answer to unmet pediatric oncologist needs (7).

The entire response to the metronomically chemotherapy was reported in 2017 in an eight-year-old kid with refractory atypical teratoid rhabdoid tumor combined with radiation treatment and surgery (continuous oral celecoxib with alternating metronomic etoposide and cyclophosphamide, combined with bi-weekly bevacizumab and monthly liposome intraterale cytarabine) (12).

Many stable tumors have been successfully paired with the vinblastine and oral cyclophosphamide. Using the regimen as replacement chemical therapy tends to enhance survival following diagnosis or replacement chemotherapy for patients with high-risk rhabdomyosarcoma (14). Because our patient had a low economic situation, we had to use metronomic chemotherapy.

In Metronomic chemotherapy, we have a multi-targeted therapy strategy. The effects of the method on tumor cells and their microenvironments are both direct and indirect. It can inhibit angiogenesis of the tumor, stimulate immune response to the cancer and lead to tumor sleep. In the 4D Effect is recognized as a new mechanism of MC. The induction of chemical-led dependency on cancer cells and forced medicinal deprivation, which takes place at treatment finishes or during pause periods, are used for metronomic chemotherapy. The medicinal dependence / deprivation action or 4D effect is referred to as this phenomenon. MC may also affect cancer cells directly (15).

We didn't find any experience of complete cure of solid tumors especially in Rhabdomyosa treated with the metronomic regimen.

The four-drug treatment scheme for refractory or re-occurring solid cancers was developed in Metro-SFCE01. Vinblastine weekly, cyclophosphamide low-dose daily, celecoxib daily and methotrexate twice weekly. In all 16 patients, low toxicity and disease stabilization associated treatment. Result of treatment was favorable (16).

Importantly, pediatric bone and soft tissue sarcomas possess unique tumor microenvironments driven by distinct molecular features. A better understanding of each malignancy's biology, heterogeneity, and tumor microenvironment may lend new insights toward immunotherapeutic such as metronomic chemotherapy.

In conclusion, rhabdomyosarcoma should be considered as differential diagnosis in all children with recurring refractory mastoiditis, especially in young children. The method for refractory response of solid tumors in pediatric oncology in LMICs is safe and cost-safer. This report makes MC clinically relevant for the concept of immunoncology and cancer immunotherapy.

CONFLICT OF INTEREST

None

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Cite this article: Gholamreza Bahoush. 2020. Complete Remission of Pediatric Rhabdomyosarcoma with Metronomic Chemotherapy. European Journal of Molecular & Clinical Medicine, 7(1), pp. 137 – 141, DOI: https://doi.org/10.31838/ejmcm.07.01.16