**Table of Contents**

### Original Articles

**Phase II/III Randomized Controlled Trial of Concomitant Hyperfractionated Radiotherapy plus Cetuximab (Anti-EGFR Antibody) or Chemotherapy in Locally Advanced Head and Neck Cancer** ................................................................. 06  
Khaled Al–Saleh, Mustafa El–Sherify, Reham Safwat, Amany Elbasmy, Jitendra Shete, Amany Hussein, Marwa Nazeeh, Ahmad Bedair

**Betel Chewing: A New Analysis, In Vitro and In Vivo, of the Risk Factors in Oral Cancer** ................................................................. 13  
Roberto Menicagli, Ortensio Marotta, Malone Nunzia, Casotti Maria Teresa

**Retrospective Analysis of Outcomes of Patients with Relapsed, Refractory and Metastatic Sarcomas who have received Metronomic Chemotherapy** ........................................................................................................... 22  
Santhosh Kumar Devadas, Sripad Banavali

**Does Adjuvant Chemotherapy for Locally Advanced Resectable Rectal Cancer treated with Neoadjuvant Chemoradiotherapy have an impact on survival? A Single Moroccan Institute Retrospective Study** .................. 29  
Youssef Seddik, Sami Aziz Brahmi, Said Afqir

**A Multicenter Study of the Impact of Body Mass Index (BMI) on the incidence of Pathologic Complete Response (pCR) Among Saudi Patients with locally advanced Breast cancer (LABC) post Neoadjuvant Chemotherapy (NAC)** .................................................................................................................. 33  

**Effects of Tualang Honey on Cancer Related Fatigue: A Multicenter Open–label Trial of H&N Cancer Patients** ........................................... 43  
Viji Ramasamy, Norhafiza binti Mat Lazim, Baharudin Abdullah, Avatar Singh

**The Incidence and Clinical Significance of Atypical Glandular Cells of Undetermined Significance on Cervical Pap Smears** ............... 52  
Ehab Al–Rayyan, Mitri Rashed, Maher Maaita, Sultan Qudah, Omar Taso, William Haddadin

**Total or Subtotal Colectomy with Primary Anastomosis for Occlusive Left Colon Cancer: A Safe, Acceptable and Applicable Procedure** ................................................................................................................ 57  
William A. Nehmeh, Michel Gabriel, Ahmad Tarhini, Ghassan Chakhtoura, Riad Sarkis, Bassam Abboud, Roger Noun, Cyril Tohmé

**Descriptive Study of Nasopharyngeal Carcinoma and Treatment Outcomes: An Eight Years Experience in Hadhramout National Cancer Centre, Yemen** ................................................................. 61  
Abdulrahman Ali Bahannan, Ahmed Mohammed Badheeb, Samir Yeslam Baithman

### Review Articles

**Preoperative Denosumab plus Surgery in the Management of Giant Cell Tumor of Bone: A Comprehensive Narrative Literature Review** ......................................................................................................... 67  
Ahmed Abu–Zaid, Sadiq Issa Alaaqil, Syed Osama Ahmad, Ibrahim Bin Hazzaa, Hani Alharbi

### Case Reports

**Malignant Pleural Mesothelioma: A Multi–Disciplinary Approach** ........................................................................................................ 76  
Muhammad Atif Mansha, Nasir Ali, Shaukat Ali, Naushaen Azam, Agha Muhammad Hamad Khan

**Stage 4S Neuroblastoma: A Report of Two Cases Presenting with Extremes of Biological Behavior** .............................................................. 81  
Mohamed Mubarak, Arbinder Kumar Singal, Ashok Gawdi

### Conference Highlights/Scientific Contributions

- News Notes.......................................................................................................................... 85
- Advertisements ..................................................................................................................... 88
- Scientific events in the GCC and the Arab World for 2019 .................................................. 89
Case Report

Stage 4S Neuroblastoma: A Report of Two Cases Presenting with Extremes of Biological Behavior

Mohamed Mubarak¹, Arbinder Kumar Singal², Ashok Gawdi³

¹ College of Medicine & Medical Sciences, Arabian Gulf University, Kingdom of Bahrain
² Department of Pediatric Surgery, MGM University of Health Sciences, Kamothe & MGM’s New Bombay Hospital, Vashi, Navi Mumbai
³ MJ Hospitals, Vashi, Navi Mumbai

Abstract

Neuroblastoma is the most common extracranial solid tumor in childhood. Stage 4S is a special stage of neuroblastoma in which majority of cases may have spontaneous regression; however, in some cases the tumor is rapidly progressive with poor prognosis and thus requires aggressive therapy. Dilemmas in its management and therapy will be discussed. We report two cases of stage 4S neuroblastoma exemplifying these two extreme behaviors. The first case is of a four–month–old baby who initially presented with a thigh lump, labial and foot nodules as well as hepatic and adrenal involvement. Following the confirmation of stage 4S Neuroblastoma with favorable histology and N–MYC negative amplification, a watchful observation approach was elected. Currently, the patient has completed two years of uneventful follow–ups with normal development. The second case is of a full–term new born baby who presented with abdominal distention and respiratory distress. Stage 4S Neuroblastoma was confirmed with an unfavorable histology and metastasis to the liver and the left adrenal gland. Due to the deterioration of the patient’s condition, chemotherapy with carboplatin and etoposide was initiated for six cycles with a good and rapid response. The patient completed two years of follow up without recurrence.

Keywords: Stage 4s; neuroblastoma; Pepper syndrome; infant

Introduction

Neuroblastoma is the most common extracranial solid tumor in infancy and 40% of patients are diagnosed before one year of age. Staging of these tumors is done in concordance with International Neuroblastoma Staging System (INSS). A special subset of these tumors – Stage 4S neuroblastoma defines a tumor occurring as a localized INSS stage 1 or 2 tumor in infants with dissemination restricted to skin, liver and/or bone marrow (<10% involvement).²³

In spite of metastasis and dissemination, stage 4S is notable because of its high propensity for spontaneous regression and high survival rate.²³ A small minority of stage 4S neuroblastomas may progress and result in a worse prognosis. Recognition and standardization of high–risk factors associated with a progressive disease and poor prognosis allows us to determine which patients need aggressive treatment from the onset and while others can be followed up with a wait and watch strategy.²³ We present two cases of stage 4S neuroblastoma that occurred in Navi Mumbai, India, which exemplify the diverse biological behavior and the dilemmas in management.

Case 1

A four–month–old female child presented with nodules over both labia for two months’ duration. The parents also noticed a nodule over the plantar aspect of the left foot and swelling of right thigh one week prior to presentation. Her physical examination was normal. The labial nodules were subcutaneous, blue in color, measuring 2x1cm and had a rubbery consistency. (Fig 1A). There was an ill–defined lump in the anterolateral aspect of right thigh but no discrete nodule was palpable. The liver was palpable 2cm below the costal margin (Fig 1A). A suspicion of stage 4S neuroblastoma was made and an ultrasound of the abdomen was performed, which revealed a right supra–renal mass with a solitary liver metastasis. A CECT scan showed a right suprarenal tumor (Fig 1B). Excision biopsy of the labial

Corresponding author: Mohamed Mubarak, College of Medicine & Medical Sciences, Arabian Gulf University. Phone No.: 00973 36512151, Email: mohdkej@yahoo.com
nodules showed a favorable histology neuroblastoma. The tumor tissue was negative for N–MYC amplification. VMA (Vanillylmandelic Acid) levels were found to be normal. 

MIBG scan (Met–Iodo–Benzy1 Guanidine) uptake was seen in the primary as well as the metastatic tumor (Fig 1C). A diagnosis of Stage 4S neuroblastoma was thus confirmed. As the patient was asymptomatic, histology was favorable and N–MYC amplification was negative, it was decided to keep the patient under observation with regular three month follow ups. Presently, the patient has completed two years of uneventful follow ups and is growing normally. On the last ultrasound examination, the adrenal lesion resolved completely and the subcutaneous nodules disappeared.

Case 2

A full–term male new born baby was brought to the emergency services with gross abdominal distension and respiratory distress. Antenatal ultrasound scans done in the second trimester and at 36 weeks were reported to be normal. On examination, the baby was tachypneic with a respiratory rate of 64/min. The heart rate was 180/min and a pansystolic murmur was heard on auscultation. The abdomen was grossly distended with a firm hepatomegaly reaching down to the left iliac fossa. Ultrasound revealed huge hepatomegaly with altered echotexture of the liver. Left suprarenal gland was noted to have a mass measuring 3x3cm. In view of a pan systolic murmur, an echocardiogram was performed which revealed a large patent ductus arteriosus (PDA) measuring 6mm with right to left shunting and congestive heart failure. CT scan showed a 2.6×3.1cm rounded hypodense left suprarenal mass with internal calcification and necrotic areas suggesting the diagnosis of neuroblastoma (Fig 2B). Also, gross hepatomegaly with numerous hypodense focal lesions suggestive of multiple metastasis were noted.

A provisional diagnosis of stage 4S neuroblastoma with liver metastases was made. Urinary VMA levels were normal. Serum ferritin levels were raised (880 ng/ml) as were serum alpha fetoprotein levels (1712 ng/ml). Intensive management in the form of oxygen by nasal prongs, fluid restriction and furosemide injections was started to control congestive heart failure. The patient subsequently improved with resolution of tachycardia and tachypnea. The abdominal distension also marginally decreased and the neonate...
started tolerating feeds. The patient was discharged after 7 days with a plan to get an MIBG scan and follow-up.

Over the next week, the baby had worsening of abdominal distension, increasing hepatomegaly and tachypnea, necessitating re-admission (Fig 2A). A repeat echocardiogram showed the PDA regression. The systolic blood pressure was noted to be persistently high for age. In view of worsening respiratory status stemming from huge hepatomegaly, a decision to start chemotherapy was taken. An ultrasound guided needle biopsy of left suprarenal mass was performed. A liver biopsy and a bone marrow aspirate from bilateral posterior superior iliac spine were also taken. Antihypertensive treatment was started with amlodipine and nifedipine. As soon as the biopsy was taken, chemotherapy consisting of 6.6mg/kg/day Carboplatin and 5mg/kg/day Etoposide (CE regimen) was started on day 17 of life over three days. The tissue from left suprarenal gland showed features of neuroblastoma with poor stroma, undifferentiated type signifying an unfavorable histology. Liver biopsy showed metastatic neuroblastoma while bone marrow was uninvolved. The MIBG scan showed uptake in the liver and in the region of left suprarenal gland (Fig 2C). Regression was observed within the next 5 days and the distress settled without requirement of ventilation which had seemed imminent at admission. The patient tolerated the regimen well initially but then developed thrombocytopenia and febrile neutropenia with gastrointestinal bleed on day eight. Conservative management and platelet transfusion led to recovery within two weeks. At three weeks, there was a significant decrease in abdominal distension and improvement in clinical symptoms and signs.

The next two courses of CE regimen were given with 50% and 25% dose reduction respectively every three weeks. A total of six courses of chemotherapy were given. Only two courses were delayed by one week each. The anti-hypertensive medications were tapered gradually and were stopped at six months of age. Also at six months of age, ultrasound showed the left suprarenal lesion to have regressed completely and there was minimal uptake over scattered areas in liver on MIBG scan. Last MIBG scan done at one and half year of age and showed no uptake in the liver or suprarenal area. The child has remained recurrence free and has completed two years of follow up. Liver function test and growth were within the normal percentiles.

Discussion

Management of stage 4S neuroblastoma ranges from watchful expectancy to aggressive therapy based on the symptomatology & risk factors for progression. Some of the factors which currently help in prognostication include age, symptomatology, MYCN gene amplification and Shimada classification of the histology of the tumor. (3-5)

Most of the infants with stage 4S neuroblastoma may not have overt symptoms due to the tumor itself and require nothing more than establishing the correct diagnosis and ascribing the risk stratification, as was done for the first case. While in other cases, liver involvement can be voluminous and lead to pressure symptoms.

William Pepper was the first one to describe massive infiltration of liver by neuroblastoma in infants, this condition is sometimes referred to as Pepper syndrome. (6) Even though most infants have a good outcome with little or no treatment even with gross liver involvement, a subset of neonates with massive hepatomegaly run a rapidly progressive course characterized by respiratory, renal, gastrointestinal impairment or coagulation disorders. This situation is typified by the second case in the present report.

Various types of treatment protocols have been described for management of this subset of neuroblastomas. The usual treatment options include low dose cytotoxic chemotherapy and radiotherapy. In massive hepatomegaly, even abdominal decompression surgery has been successfully used to pass over the respiratory crisis. (7) Furthermore, there have been reports of hepatic artery embolization along with radiotherapy and chemotherapy for aggressive 4S neuroblastomas with good results. (8)

In the present report, both cases were N–MYC amplification negative and given the high chances of spontaneous regression, a wait—and—watch approach was initially elected at diagnosis. The second case had symptoms of congestive heart failure which partly responded to supportive measures and the baby was discharged. Re-admission and requirement of therapy was primarily mandated by a rapid deterioration due to massive hepatomegaly. Also, this child was less than two months of age at presentation and had an unfavorable histology making it a high—risk case.

Chemotherapy remains the initial line of therapy for high risk and symptomatic tumors. In a large review study by French Society of Pediatric Oncology (SFOP), results of liver irradiation and various types of chemotherapeutic protocols were discussed in stage 4S neuroblastoma requiring therapy. (9) The first line regimens included cyclophosphamide—vincristine regimen or carboplatin—etoposide regimen; the CE regimen was found to have a rapid and superior response in the study. In case 2 of the present study, CE regimen was started on day 17 of age and a rapid response was observed within the first week itself. There was significant hematological toxicity observed in the first cycle but was controlled with dose reduction in subsequent cycles. There was no other toxicity observed and the child has remained well at two years’ follow—up, underlining the safety and efficacy of CE regimen as a first line therapy in such cases. Second line treatment schedules in the French
Stage 4S Neuroblastoma: Two Cases Presenting Extremes of Biological Behavior, Mohamed Mubarak, et al.

study consisted of the CADO regimen (cyclophosphamide, vincristine, doxorubicin), etoposide–cisplatin regimen or high–dose chemotherapy (Busulphan–melphalan, BCNU–VM26–carboplatin, or carboplatin–melphalan) followed by autologous bone marrow or peripheral stem cell rescue. Fortunately, these were not required in the present case.

To conclude, stage 4S neuroblastoma remains an enigmatic tumor which can have extremes of biological behavior. While majority of cases remain just diagnostic queries and require observation, there are some which require therapy. The therapy has to be individualized for each case and overall, symptomatology remains the single most important factor mandating intervention.

Acknowledgements

We would like to thank Viral Jain, Vijay Kadam and Pankaj Deshpande for their contributions towards this case report.

References