Spontaneous regression of a > 5cm infant neuroblastoma after a three-fold volume increase without life or organ threatening features

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Abstract

Spontaneous tumour regression is a well-recognised phenomenon in infantile favourable-biology neuroblastoma. An 'expectant-observation' strategy avoids chemotherapy or surgery associated risks but has mostly been limited to small tumours (diameter < 5 cm) and discontinued if significant tumour growth or increasing catecholamine levels. Here we report the successful use of an observation-only strategy in an infant with unresectable neuroblastoma > 5 cm at diagnosis which initially tripled in size with a 10-fold increase in urinary catecholamines. We highlight the need for consensus evidence-based criteria to define the subgroup where a 'wait-and-see' approach is appropriate and criteria to begin active treatment.

INTRODUCTION

Neuroblastoma (NB) is the most common malignancy of infancy.[1] Spontaneous tumour regression is a well-recognised phenomenon in low-risk, favourable-biology cases.[2] Complete regression may occur well after the first year of life.[2,3]

Several groups have demonstrated the safe use of a 'wait-and-see', observation-only strategy for low-risk infants with favourable biology.[3–12] This approach avoids risks associated with unnecessary surgical and cytotoxic treatments, but no international consensus on definition or criteria for treatment exists. The approach has generally been limited to cases with small tumours (diameter < 50 mm at diagnosis) and active treatment generally started if a significant increase in tumour size or tumour markers were observed.[5–12]

We discuss a case of an infant with NB where an observation-only approach was successfully used despite a > 5 cm tumour diameter at diagnosis which tripled in size with a 10-fold increase in urinary catecholamines, before undergoing spontaneous tumour regression.

CASE DESCRIPTION

A 5-month-old girl presented with suspected bronchiolitis, vomiting, adenovirus positive bloody diarrhoea and an abdominal mass. An ultrasound scan confirmed a left heterogeneous suprarenal mass (70 x 40 mm) with internal calcification crossing the midline with recognised imaging characteristics of NB of vascular encasement of both the aorta and superior mesenteric artery.

Urinary catecholamines were elevated; 4-hydroxy-3-methoxymandelic acid (HMMA) to creatinine ratio of 31.8 (0-12) and 4-hydroxy-3-methoxyphenylacetic acid (HVA) to creatinine ratio of 35.9 (3-15). Magnetic resonance imaging (MRI) demonstrated a peripherally enhancing bosselated multinodular mass (62 x 70 x 79 mm; 178 ml) displacing the left kidney and encasing the left renal pedicle**(Fig. 1A**). Tumour volume was calculated using the formula, volume = $(\pi/6)$ × antero-posterior (depth) × width × cranio-caudal

measurements.[13] Completion staging with computed tomography (CT) showed no intracranial or pulmonary metastatic dissemination with a metaiodobenzylguanidine (MIBG) scan showing localised uptake at the primary site with no focal bony uptake/ dissemination. An ultrasound guided biopsy confirmed favourable histology using the International Neuroblastoma Pathology Classification (INPC), without *MYCN* amplification, with triploidy and no segmental chromosomal abnormalities (SCAs) (favourable biology) (**Fig. 2A-D**).

A diagnosis of low-risk, localised, unresectable, stage L2 neuroblastoma was made as per the International Neuroblastoma Risk Group Staging System (INRGSS).[14] For patients aged < 18 months at diagnosis with L2 neuroblastoma, no SCAs and no life or organ threatening features, a close surveillance strategy using 3 monthly interval MRI scans and urinary catecholamine monitoring is indicated.[15]

Surveillance MRI performed at 3 months, demonstrated interval increase in tumour size and volume (71 x 100 x 97 mm; 358 ml) including a central area of necrosis. However, the child remained asymptomatic, so ongoing 3 monthly MRI surveillance was planned\sout.

Five months after diagnosis, there was a > 9-fold increase in urinary catecholamines. Active treatment with chemotherapy was considered because of substantial tumour growth and increasing tumour markers **(Fig. 1D-E).** However, symptoms remained mild and after discussion with the family, close observation was continued.

A third MRI, 6 months after diagnosis, showed ongoing tumour growth (77 x 110 x 130 mm: 572ml, with a 50 x 50 mm central area of tumoural necrosis) and displacement of the left kidney but no hydronephrosis. Urine catecholamines had increased further to > 10-13 x the diagnosis levels. Despite worsening radiological and biomarker trends, the child was now completely asymptomatic.

Nine months after diagnosis, MRI scanning showed further interval tumour growth but for the first time, a reduction of urinary catecholamines (**Fig. 1D**). An MRI scan 12 months after diagnosis for the first time showed measurable reduction in tumour size in all 3 planes and with urinary catecholamine levels continuing to fall.

Subsequent serial MRI scans at 16, 21, 27, 33 and 43 months showed continued tumour regression followed by stabilisation. Urinary catecholamines returned to the normal range 28 months after diagnosis and have remained normal since then (**Fig. 1D-1E).**

DISCUSSION

Spontaneous tumour regression is well recognised in Infants with low-risk neuroblastoma and favourable biology (i.e. no SCAs and hyperdiploidy).[2] The concept of a 'wait-and-see' approach has been described previously and avoids the morbidity and mortality associated with chemotherapy and potentially extensive surgery.[3,5–11,16] However, there is currently no international consensus about which cases this observational approach is appropriate for, and what criteria should be used to define progression requiring active intervention.

Yamamoto *et al.* defined criteria for using an observation-only approach for small lesions detected in a Japanese population screening programme in 1998.[12] Subsequent publications have cited these same criteria or adapted versions which have generally only included tumours < 5 cm in diameter at diagnosis.

In 2007, the German Society of Paediatric Oncology and Haematology published data showing that spontaneous regression in non-*MYCN* amplified, localised neuroblastoma may start after 1 year of age, and occur in patients with larger tumours, suggesting that a 'wait-and-see' strategy may be more widely appropriate.[3]

A 2012 Children's Oncology Group (COG) study demonstrated the safe and effective use of 'expectant-observation' in Stage 1 and 2 adrenal tumours in patients less than 6 months old.[7] However, this study used conservative tumour diameter cut offs of 3.1 cm or 5 cm for solid and cystic tumours respectively. Additionally, 'expectant-observation' was terminated if tumour volume increased by 50% or if catecholamine levels increased above 50% and did not return to baseline within 12 weeks. A phase III COG trial is currently

investigating an observational approach using response and biology-based risk factor-guided therapy in infants < 18 months with L2 tumours and favourable biology. In this trial, a 25% increase in tumour volume prompts use of adjuvant therapy.[17]

In the current case, the initial tumour size and the observed growth (100% increase in anteroposterior diameter, 57% in transverse diameter and 67% in craniocaudal diameter), resulting in a > 3 fold increase in tumour volume, along with 9-10 fold increase in HMMA and HVA, would have precluded a 'wait-and-see' strategy based on previous study criteria.[6,7,12] Persevering with an observational approach, with parental agreement, in the absence of life- or organ-threatening features, avoided the risks of active treatment while still achieving a positive clinical outcome. However, it is critical to consider patient tumour biology and clinical features before embarking on an observation-only strategy. Utilising pan-genomic techniques such as SNP (single nucleotide polymorphism) arrays and more recently whole genome sequencing (WGS) allows SCAs conferring a higher risk of progression and relapse to be excluded.[18] Age at diagnosis is also important as some groups e.g. infants < 2 months of age with MS disease, have the potential for rapid deterioration and may benefit from early treatment regardless of biology.[19]

This case demonstrates that a 'wait-and-see' approach may be more widely applicable than previously used, including tumours > 5 cm in diameter at diagnosis. This case also illustrates that in patients with favourable biology without life- or organ-threatening features, tumour growth and rising catecholamines, do not by themselves preclude safe continuation of an observation-only approach.[3]

Further work is required to establish international evidence-based criteria to identify subgroups of patients where embarking on an observational approach is appropriate and to review criteria for active treatment when using this initial management strategy.

Conflict of Interest

None declared.

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LEGENDS

FIGURE 1. *Monitoring of tumour during observation*

(A-C) Serial magnetic resonance imaging Large (62 x 70 x 79 mm; 173 ml) peripherally enhancing bosselated multinodular mass in the left suprarenal fossa extending across the midline, displacing the left kidney, and encasing the left renal pedicle. The right renal pedicle is also encased but to a lesser degree. There is retroaortic extension of the mass which abuts and displaces the IVC and totally encases the superior mesenteric artery. Some presumed nodal deposits also identified.

(D) Change in tumour dimensions during 45 months of observation.

(E) Urine catecholamine (HMMA and HVA) trends during 45 months of observation.

FIGURE 2. *Diagnostic testing*

(A) Tumour histology (40x magnification). Small round blue cells infiltrating stromal tissue. Tumour cells show scant cytoplasm with hyperchromatic nuclei set in a delicate fibrillary neuropil without ganglionic differentiation. The mitosis-karyorrhexis was low (<2%). This is poorly differentiated neuroblastoma - age <1.5 years and low MKI (<2%) i.e. INPC favourable histology.

(B) WGS Circos plot showing whole chromosomal aberrations and absence of significant structural variants e.g. *TERT*rearrangement, no pathogenic small somatic or germline variants were identified.

(C) WGS mutational signature showing absence of known pathogenic signatures.

(B) SNP array of tumour showing overall triploidy with trisomies for chromosomes, 2, 5, 6, ,8, 9, 10, 12, 14,15,16 tetrasomies for chromosomes 1, 4,13 pentasomy for chromosomes 7, 17, diploidy for chromosome 11 and monosomy for chromosome 3. Upper panel log2ratio, lower panel B allele frequency (3N, +1, +4, +13, +7, +7, +17, +17, -11, -3, -3) i.e. 73.

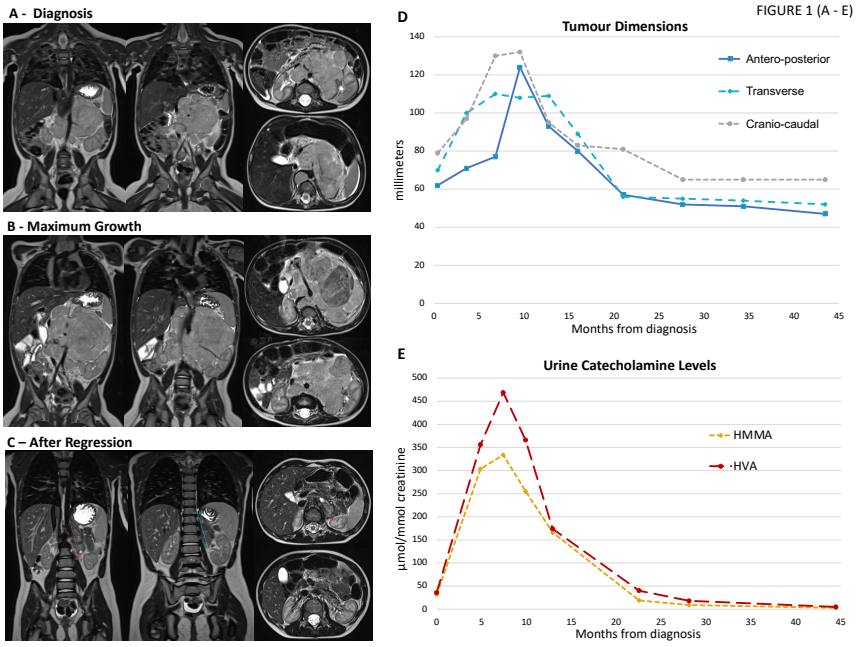

FIGURE 2 (A – D)