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A FOCAL LESION IN THE FALX CEREBRI: HARBINGER OF CLASSIC STAGE 4 NEUROBLASTOMA IN AN INFANT CURED DESPITE RESIDUAL DISEASE AFTER MINIMAL THERAPY

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Abstract

An asymptomatic 11-week old received no treatment after he was classified as having a suspected atypical form of *MYCN*-nonamplified hyperdiploid stage 4S neuroblastoma (NB), with masses in an adrenal gland, subcutaneous tissues, and the falx cerebri. Within two months, however, disease progressed in dura and bone marrow. Two cycles of low-dose chemotherapy achieved a partial response; treatment was discontinued. Complete remission was documented 24 weeks post-cycle 2, and has continued >6 years. The falx cerebri probably does not represent an atypical site for stage 4S NB, but stage 4 NB with favorable biology is sometimes curable with minimal therapy.

Keywords

falx cerebri; MIBG; minimal therapy

INTRODUCTION

Infants with *MYCN*-nonamplified metastatic (stage 4) neuroblastoma (NB) have long-term event-free survival (EFS) rates of >80–90%;^{1–3} the key issue, given late toxicity concerns, is to what extent therapy can be reduced without affecting the high cure rate. Successive national studies using 9-month moderate-dose¹ and 4–8 cycle low-dose^{2,3} protocols,

respectively, achieved comparable success. The contrasts with other pediatric solid tumors are striking in that the latter, when metastatic to bone or bone marrow (BM), are rarely curable even with high-dose chemotherapy.

We reported long-term EFS of this subset of NB patients despite stopping therapy in the presence of residual disease.⁴ The experience pointed to a tendency for delayed response, and undercut the standard practice of continuing chemotherapy or adding radiotherapy in order to achieve complete remission (CR). We describe a case of widespread NB in an infant with the distinctly rare finding of a mass in the falx cerebri. Cure was achieved with minimal therapy.

CASE REPORT

An 11-week old boy was evaluated for right pre-auricular and left antecubital masses. Excisional biopsy of the antecubital mass revealed NB with favorable histology, no amplification of the *MYCN* oncogene, and hyperdiploidy (DNA index 1.4). BM histology and bone scan were normal. Computed tomography (CT) showed a suboptimally visualized left adrenal mass, subcutaneous nodules, and a 9.4×6.4 mm expansile lesion within the anterior cephalad aspect of the falx cerebri (Figure 1). ¹²³I-metaiodobenzylguanidine (MIBG) scan was positive in the adrenal, preauricular, and falx cerebri masses, as well as the right femur. Magnetic resonance imaging (MRI) of the latter showed BM but no cortical bone disease. The pre-auricular mass was resected and proved to be NB (DNA index 1.4) in subcutaneous tissue. Treatment was deferred based on the rationale that this asymptomatic baby had an atypical form of stage 4S NB (small main mass, skin nodules, no cortical bone metastases, <10% BM involvement)⁵ with favorable biology – an entity with a high rate of spontaneous regression.^{6–8} However, by 7 weeks from diagnosis, urine catecholamine levels were 20% higher, NB was seen histologically in BM, head MRI revealed new dural thickening and extraosseous extension (with possible early cortical bone invasion), and the adrenal mass had enlarged to 3.7×2.0×2.7 cm. The MIBG scan continued to show uptake in the right femur, adrenal tumor, and the falx but new uptake in the left femur and tibia was present (Figure 2). The now 19-week old patient began treatment according to the Children's Oncology Group (COG) A3961 protocol for intermediate-risk NB.² Cycles 1 (carboplatin 540 mg/m² and etoposide 360 mg/m²) and 2 (carboplatin 540 mg/m², cyclophosphamide 33 mg/kg, and doxorubicin 30 mg/m²) achieved a partial response (>50% decrease in all disease parameters). Therapy was discontinued. The MIBG scan was normal and cranial disease was markedly reduced at 2.5 months post-cycle 2. CR was documented 9 months post-cycle 2 and has continued 78+ months from diagnosis.

DISCUSSION

This child developed osteomedullary metastatic NB, yet was cured with only 2 cycles of low-dose chemotherapy. Moreover, NB was still present when treatment was stopped. At presentation, the baby appeared to have an atypical form of stage 4S NB with favorable biology which is renowned for a propensity to regress spontaneously. This remarkable phenomenon is seen in 40–50% of patients in recent reports^{6–8} and is thought to reflect, not

metastatic disease, but rather a multifocal process involving tumor cells with limited proliferative potential and apoptotic programming.⁹

The discovery of a falx cerebri mass raised concern about stage 4 NB, for which chemotherapy is standard of care. A wait-and-see approach was tried, consistent with a recently advocated strategy to observe asymptomatic infants who have *MYCN*-nonamplified NB that, by strict criteria, represents stage 4 but may have stage 4S biology and natural history.^{9,10,11} These infants lack the cortical bone metastases and extensive BM invasion of classic stage 4, but have unresectable tumors, evidence of NB in BM by MIBG scan, and/or NB in atypical distant sites such as pleura. The view was that the falx cerebri might constitute another atypical site of stage 4S; our patient's clinical course suggests otherwise. The literature is not helpful in resolving the issue: The sole prior report of a NB falx lesion without widespread intracranial disease involved an asymptomatic 5 month old with clinical findings suggestive of stage 4S (adrenal, skin, and liver lesions) who was cured after receiving low-dose chemotherapy and radiotherapy to the falx.¹² In another report, an asymptomatic 6 month old had typical stage 4S findings (adrenal and skin lesions) except for a large intracranial mass obscuring the falx; after low-dose chemotherapy, CT showed only slight calcification of the falx, and he was cured.¹³

In opting for a wait-and-see approach, we also took into account our experience with an infant who had a paraspinal NB and radiologic evidence of leptomeningeal disease but no osteomedullary metastases and did well without cytotoxic therapy.¹⁴ A recent report described spontaneous regression of widespread NB, including a meningeal lesion, in an infant.¹⁵ Our "expectant observation" approach also applied to our patient's adrenal mass: surgical resection of small adrenal NBs detected by age 6 months is no longer recommended since these masses, whether with (stage 4S) or without (stage 1) distant disease, usually regress spontaneously.^{16,17}

In our patient, progressive disease in bone, dura, BM, and abdomen responded to 2 cycles of low-dose chemotherapy, and residual NB disappeared within months. This clinical course illustrates the potential to minimize therapy in infants with biologically-favorable widespread NB. Low- or moderate-dose chemotherapy might also suffice for similar patients who are diagnosed at 12–18 months of age, which is just beyond the long-standing clinical prognostic divider of age 365 days. These patients have an excellent prognosis with the aggressive multimodality therapy (including stem-cell transplantation) routinely used for high-risk NB.^{18,19} However, their age and tumor biology, plus anecdotal cases of long-term EFS of such patients treated with surgery alone, an intermediate-risk protocol, or intensive chemotherapy without stem-cell transplantation,¹⁸ suggest that they will do well with relatively non-toxic treatment approximating that used successfully in patients in a slightly younger age bracket (i.e., infants). COG is currently testing that hypothesis.

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Figure 1.
Computed tomography showing lesion in falx cerebri.

Figure 2.
 ^{123}I -MIBG scan (A–P and P–A views) showing widespread disease including in left adrenal area, head (falx), both femora (right greater than left), and left tibia. Physiologic uptake in the parotid gland, liver, and heart is also seen.