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Case Report: Open Access

A Case of Localized Neuroblastoma in Caffey Disease, with Early and Uncommon Progression

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Abstract

Background: Caffey disease is a rare syndrome caused by mutation in the alpha-1 collagen type I gene, not described in literature as a predisposing condition to cancer development.

Observation: We report a case of a 6-years-old female diagnosed with Caffey disease that developed a localized neuroblastoma. The patient had a poor clinical and radiological response with unusual disease dissemination and progression until death.

Conclusion: The case is a rare example of rapid progression of localized neuroblastoma in a patient with Caffey disease. A probable predisposition to neoplasm in this syndrome or atypical tumour evolution must be confirmed by other clinical observations.

Case Report

We report on a female infant, born from spontaneous delivery at 39 weeks gestation, by normal pregnancy. Apgar scores were 10 at 1 and 5 min. Physical examination was normal, except for a thickening involving bilateral tibiae. Blood count, infection index and abdominal ultrasound imaging were normal. Family history revealed that maternal grandmother and three cousins (brothers each others) suffered from Caffey disease. The genetic medical team made a diagnosis of familial infantile cortical hyperostosis at birth, based on clinical evidence and familiar anamnesis. Three months later the patient developed a tender and warm thickening involving the mandible, due to cortical hyperostosis. All osseous lesions had spontaneous regression in few months, confirming the diagnosis of self-limiting disease. The patient continued the follow-up and she did not develop any other symptom during the following six years.

In February 2006 the patient came at our attention for enlarged abdomen. CT scan showed hypodens abdominal mass (15x12x18cm), arising from the left adrenal gland, crossing the midline, with "mass effect" on spleen, stomach, pancreas, liver and compressing celiac tripod, mesenteric and renal arterials. Inferior cava vein and aorta were encased by tumour and the left kidney dislocated on the pelvis, without infiltration sign. Total body MIBG-scintigraphy showed mild hyperactivity on left abdomen.

Catecholamines and urinary metabolites were high: homovanillic acid (HVA) 14.2mg/24h (n.v. 0-5.4), vanillylmandelic acid (VMA) 10.8 mg/24h (n.v. 0-3.5). Neuron specific enolase (NSE) 28ng/mL (n.v.<14), ferritin 3873ng/mL (n.v. 12-110).

Histology on surgical biopsy diagnosed undifferentiating neuroblastoma, poor stroma, intermediate mitotic-karyorrhexis index and multiple necrosis focus. Analysis of n-MYC amplification showed n-MYC gain. Bone marrow cytology was normal.

The patient was treated according to the "European SIOP - AIEOP Unresectable Neuroblastoma Chemoterapy Protocol" [1], INSS stage III [2], for 4 months, with two courses of carboplatin (200mg/mq) and etoposide (150mg/mq), given on day 1 to 3, with interval two courses of cyclophosphamyde (300 mg/mq), on day 1 to 5, doxorubicin (30mg/mq), on day 4-5, vincristine (1.5mg/mq), on day 1 and 5.

We observed a partial clinical and radiological response and the patient underwent two further courses of topotecan (1.5mg/mq), on day 1 to 5, vincristine (2mg/mq) and doxorubicin (45mg/mq), given on day 4-5 (48 hours continuous infusion) [3]. Two weeks after chemotherapy, total body MIBG-scintigraphy showed abdominal hyperactivity reduction, CT images revealed stable abdominal mass, biohumoral parameters persisted moderately altered. The patient was in very good clinical conditions. Since the persistent residual mass unresectability, a second surgical biopsy was performed and histology evidenced nodules of neuroblastoma vital cells (80% of tissue) and necrosis (20%). Because of poor histological response, the patient underwent two adjunctive ^{131}I-MIBG-radio metabolic treatments.

Subsequent disease evaluation showed increasing catecholamines and total body MIBG-scintigraphy revealed two new areas of hyperactivity on right femur. CT scan evidenced multiple hypodens

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hepatic nodules (maximum diameter 4cm) and right pulmonary nodules: all these lesions were negative at MIBG-scintigraphy. Furthermore we found neuroblastoma bone marrow infiltration.

The patient received further treatment (two courses of gemcitabine 1000mg/mq and oxaliplatin 100 mg/mq on day 1 of a 14-d cycle) [4], but a sudden clinical failure occurred, with asthenia, fever, inguinal and abdominal pain, severe haematological and hepatic toxicity, increasing inflammatory and cytolysis index. The patient presented ascites, bleeding, persistent pancytopenia, dyspnea and severe abdominal pain. Exitus occurred within few days.

This case is an example of rapid and unusual progression of localized neuroblastoma. Metastatic lesions were early, simultaneous, widespread (skeleton, liver, lung, bone marrow) and MIBG-negative (except for bone lesions) and we suppose that neoplastic cells became more undifferentiated during the treatment. Outcome of localized neuroblastoma without n-MYC amplification is good. International studies report 90% survival rate in some groups of patients with primary chemotherapy and radical surgery [1]. Prognosis remains poor for non-responder patients, metastatic neuroblastoma, n-MYC amplification [5,6].

Furthermore, that uncommon tumour progression occurred in a young patient affected by Caffey syndrome, a rare disease affecting various skeletal elements and contiguous connective tissue (*OMIM 114000)* [7], not described in literature as a predisposing condition for cancer development.

Infantile cortical hyperostosis (ICH), also known as Caffey disease, Caffey-Silverman or Smyth syndrome, is a genetic self limiting bone disorder of early childhood characterized by acute inflammation of soft tissues and localized thickening of the underlying bone cortex [8]. Diagnosis may be delayed as this disorder mimics a wide range of diseases (osteomyelitis, hypervitaminosis A, scurvy, bone tumours, metastatic neuroblastoma, iatrogenic administration of prostaglandins E1 or E2, severe chronic hypoparathyroidism, hyperphosphatemia and child abuse) [9,10].

This rare collagenopathy has been reported to occur in familial and sporadic forms, in infantile or prenatal disease. The familial form is transmitted as an autosomal dominant trait with incomplete penetrance: from Gensure et al. genetic linkage studies, the affected individuals and obligate carriers are heterozygous for a missense mutation in the COL1A1 gene which results in a recurrent arginine-to-cysteine substitution (R836C) in the α1(I) chain of type I collagen (COL1A1 gene) [11-14]. Moreover, Ueda et al. [15] have described non-familial cases attributed to PGE therapy as prevention of duct closure in ductus-dependent cyanotic heart diseases [15].

The prenatal form is rare and can occur after 35 weeks of gestation in the benign form, usually without any major sequelae, or before 35 weeks of gestation in the severe form, often lethal [16]. The bone lesions, recognized radiologically on average by 27 weeks of gestation, are often associated to maternal polyhydramnios, hydrops, anasarca, hepatomegaly, pulmonary hypoplasia and significant long bones abnormalities with major angulations of long bones (tibia, ulna, femur, ribs) and jaws (75-80%), spontaneous abortus, premature delivery, sudden death for cardiac arrest after birth. The newborns present an unusual facial profile with mild micrognathia, short arms and legs, small rigid bellshaped chest; leukocytosis, increased serum levels of hepatic enzymes and biochemical inflammation markers are frequent [7].

The infantile form becomes clinically evident at 5-7 months of life with hyperirritability often accompanied by fever and anorexia, quickly followed by painful, firm, soft tissue swelling. Bone lesions are often asymmetric with involvement of the mandible (70-90% of the cases), the clavicle (in half the cases), the ribs and the scapulae (20–30%). In the long bone (mostly the tibiae) the lesions are localized in the diaphysis resulting in grossly deformed spindle shaped [17,18]. Laboratory findings include elevated erythrocyte sedimentation rates and alkaline phosphatase levels along with leukocytosis (mainly due to neutrophils), anemia, and increased C - reactive protein and immunoglobulin levels suggesting a concurrent inflammatory distress [19]. Radiological findings (periosteal elevation, new bone formation and cortical thickening involving the diaphysis of bilateral tibia, ulna and femur) are diagnostic. The disease is usually self-limiting, with severe symptoms lasting from 2-3 weeks to 2-3 months and spontaneous regression by two years. However, periods of exacerbations and remissions frequently occur, at identical and distant sites, in the first 2 or 3 years of life and several well documented cases of recurrence of cortical hyperostosis during adolescence have also been reported [18,19]. Outcome is unpredictable and sometimes characterized by a protracted clinical course: tubular bones may be deformed with osseous bridges between adjacent bones, synostoses, scoliosis mild leg-length discrepancy, long bone angular deformity, facial asymmetry, and small stature have also been described [10,20].

In our patient, familial data and clinical findings allowed to diagnose familial infantile Caffey disease, evident at birth: in particular she had typical lesions involving bilateral tibiae and mandible, with spontaneous complete regression, as usual in this condition. Reviewing this case, we considered a different hypothesis, if the patient had some form of neuroblastoma from birth, which later dedifferentiated. Congenital neuroblastoma usually involves only bone marrow, liver, skin, without any osseous lesion [2,5]. Clinically hyperostosis could mimic bone metastatic neuroblastoma, but in this tumour, osseous lesions appear radiogically as lithic areas and are MIBG positive in most cases [2,5,6]. Abdominal imaging in our patient showed normal adrenal gland and hypochondriac organs at birth and abdominal clinical evaluation was normal during the 6-years-follow-up. The skeletal sites involved by Caffey disease in our patient were different from the ones involved by neoplastic cells when she had tumour progression after the first line of chemotherapy.

Reports of neuroblastoma in patients with Caffey disease are not described in literature. A probable predisposition of neoplasm in these patients or atypical presentation/evolution of tumour must be confirmed by other clinical observations.

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