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LETTER TO THE EDITOR
Neuroblastoma Stage 4S With ^{123}I-MIBG-Positive Bone Marrow Involvement

To the Editor: Neuroblastoma stage 4S, a unique subtype of neural crest derived tumors, occurs by definition only in children less than 1 year of age [1]. The hallmark of this embryonal neoplasm is a high rate of spontaneous regression in young patients with localized and disseminated disease. In stage 4S patients, metastases are usually confined to the liver, bone marrow, and skin, while the extent of bone marrow involvement remains by definition less than 10% and is usually minimal [2]. According to the International Neuroblastoma Staging System's (INSS) definition, demonstration of bone marrow lesions by Iodine^{123}-metaiodobenzyl guanidine (^{123}I-MIBG) scintigraphy excludes stage 4S disease [2]. In the case we describe, however, bone marrow involvement was detected by MIBG scan, but clinical behavior of a stage-4S tumor was nevertheless evident.

A tumor of the right adrenal gland ($5 \times 5 \times 5$ cm) was diagnosed in a newborn female. Vanillylmandelic acid (VMA) in serum (707 ng/ml, normal <214) and urine (62 nmol/μmol of creatinine, normal <20) as well as neuron-specific enolase (NSE, 87.8 ng/ml, normal <20) in serum were markedly elevated. Homovanillic acid (HVA) levels in serum and urine were in the normal age group. Abdominal ultrasound and magnetic resonance tomography also revealed a left adrenal gland tumor ($4 \times 2 \times 3$ cm), but indicated no involvement of the liver. ^{123}I-MIBG scintigraphy with 35 MBq disclosed strong radionuclide accumulation in the right adrenal region, but no osteomedullary involvement. The girl was diagnosed with multifocal neuroblastoma and subsequently followed as an observation patient, as recommended by the NB-97 trial [3].

Due to progressive tumor growth, sweating, abdominal pain, tachycardia, and arterial hypertension, the right adrenal tumor ($7 \times 8 \times 5$ cm) was surgically removed when the patient was 10 weeks of age. Histology revealed a poorly differentiated, stroma-poor neuroblastoma with a low mitosis karyorrhexis index. During surgery, infiltration of the left adrenal gland and the liver was observed and subsequently confirmed histologically by the biopsy of both regions. The tumor showed absence of *MYCN* amplification (one *MYCN* copy per haploid genome) and no deletion of 1p36, but did have deletion of 11q23 by fluorescence in situ hybridization. It expressed the markers trkA and CD44 by immunohistochemistry. At that time bone marrow aspirates showed GD2 positive tumor cell infiltration of less than 5%. ^{123}I-MIBG scintigraphy with 40 MBq prior to surgery revealed tracer accumulation in both adrenal regions, femora and tibiae, compatible with bone marrow involvement (Fig. 1). At 1 year of age, without having been treated with chemotherapy, the girl remained in excellent clinical condition. The left adrenal tumor regressed and liver metastases were

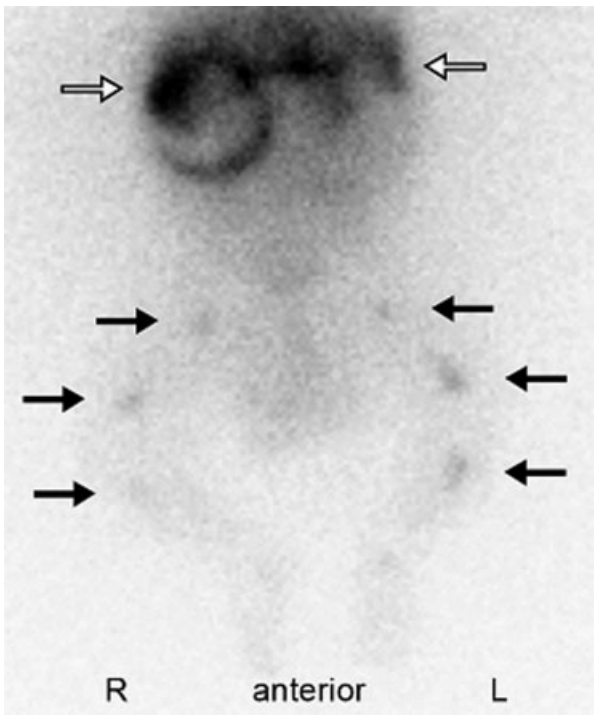

Fig. 1. ^{123}I-MIBG 40 MBq scintigraphy in the patient at 2 months of age with tracer accumulation in projection of the adrenal glands (white arrows) and the bone marrow (black arrows) of both femora and tibiae (anterior view; R stands for right and L for left side).

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absent. Additionally, VMA and NSE returned to normal values. ^{123}I-MIBG scintigraphy repeated with 80 MBq showed no tracer accumulation at the age of one year.

Independent retrospective review was performed of the first two ^{123}I-MIBG scans done at 2 weeks and at 2 months of age. At the latter time point, a minimal tracer accumulation over proximal and distal femora and proximal tibiae was confirmed. However, both scans had been performed with a lower tracer concentration than the minimum recommended 80 MBq in the study protocol, based on published guidelines [4].

It may, therefore, be argued that if 80 MBq MIBG had been used, the bone marrow lesions would have manifested themselves more prominently. As a consequence, the patient would have been classified with stage 4 disease and treated with chemotherapy at least according to intermediate risk protocols, as recommended currently by most international study groups. Despite an MIBG tracer accumulation in the bone marrow, which has the highest sensitivity in detecting osteomedullary involvement [5], the clinical course reported here clearly argues in favor of a stage-4S patient. Further evaluation of infants with positive ^{123}I-MIBG uptake of bone marrow is warranted in order to reevaluate the prevailing view that scintigraphic osteomedullary involvement in neuroblastoma excludes these patients from allocation to stage 4S.

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REFERENCES

1. Brodeur GM. Neuroblastoma: Biological insights into a clinical enigma. Nat Rev Cancer 2003;3:203–216.
2. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11:1466–1477.
3. Simon T, Spitz R, Faldum A, et al. New definition of low-risk neuroblastoma using stage, age, and 1p and MYCN status. J Pediatr Hematol Oncol 2004;26:791–796.
4. Olivier P, Colarinha P, Fettich J, et al. Guidelines for radioiodinated MIBG scintigraphy in children. Eur J Nucl Med Mol Imaging 2003; 30:B45–B50.
5. Labreveux de Cervens C, Hartmann O, Bonnin F, et al. What is the prognostic value of osteomedullary uptake on MIBG scan in neuroblastoma patients under one year of age? Med Pediatr Oncol 1994; 22:107–114.