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ORIGINAL ARTICLE

Evaluation of morphological/immunohistochemical versus nuclear medicine imaging modalities in detecting metastatic bone and/or marrow deposits in neuroblastoma patients

Amr El-Sayed Zaher [a,*], Ahmed M. Zaher [b], Manar M. Moneer [c], Basma M. El Gamal [a]

[a] *Clinical Pathology Department, National Cancer Institute, Cairo University, Egypt*
[b] *Nuclear Medicine Unit, Department of Radiotherapy and Nuclear Medicine, National Cancer Institute, Cairo University, Egypt*
[c] *Department of Epidemiology and Biostatistics, National Cancer Institute, Cairo University, Egypt*

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KEYWORDS

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Abstract *Background & Purpose:* In planning diagnostic or follow-up investigational strategies, neuroblastoma (NB) metastatic deposits in bone and/or bone marrow (BM) should be detected as early as possible. Therefore, all investigational detection tools should be conducted simultaneously for precise staging. However, because of the financial conditions in our developing countries and in view of the cost/benefit relationship, the question is, can one detection tool only become satisfactory and replacing others? The purpose of our study is to compare simultaneous results of bone and metaiodobenzylguanidine (MIBG) scans versus BM biopsies with immunohistochemical (IHC) staining; in detecting bone and/or BM metastatic deposits in NB patients.
Material and methods: This study included 138 NB patients; 46 were de novo and 92 were under follow-up. They were subjected to bilateral BM biopsies, IHC staining (using NSE McAb) and

* Corresponding author. Address: Haematology Unit, Clinical Pathology Department, National Cancer Institute, Cairo University, 6th Ahmed Mekhemar St., Nozha El-Gedida, Cairo, Egypt. Tel.: +20 2 26248379, mobile: +20 101412286.
E-mail address: amr_zaher_66@yahoo.com (A. El-S. Zaher).

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Tc-99m methylene diphosphonate (Tc-99m MDP) bone scan (BS). Only 57/138 patients were, in addition, subjected to I-131 MIBG scan.

Results: Matched results between IHC-stained BM sections and bone scans (BSs) 107/138 (77.5%) were higher than the un-matched ones 31/138 (22.5%). There was a moderate agreement between the two methods in all studied cases (Kappa = 0.538) and it was higher among de novo (Kappa = 0.603) than follow-up group (Kappa = 0.511). Among the 31 un-matched results, the most frequent (17/31) were due to the presence of minute amount of infiltrating NB cells that could be detected by IHC-stained BM sections and not by BSs. The less frequent (12/31) were due to the presence of metastatic deposits outside pelvic bones that could be detected by BSs and not by IHC-stained BM sections mainly in the follow-up cases (11/12) rather than de novo cases (1/12). The matched results between IHC-stained BM sections and MIBG scans 54/57 (94.7%) were higher than the un-matched ones 3/57 (5.3%). The agreement between the two methods was higher among de novo (Kappa = 1.000) than follow-up group (Kappa = 0.847). The agreement between IHC-stained BM sections and MIBG scans was substantial (Kappa = 0.890) while that between IHC-stained BM sections and BSs was moderate (Kappa = 0.538).

Conclusions: We suggest a step-wise strategy to be applied, at least in developing countries, in approaching de novo and follow-up NB cases for detecting bone and/or BM metastatic deposits. This strategy might be beneficial if it is considered during application of NB guide-lines for diagnosis and follow-up.

Introduction

Bone and/or bone marrow (BM) involvements often occur in patients with neuroblastoma (NB). Therefore, a reliable specific and sensitive tool for tumor cells detection at these areas will significantly influence the diagnosis, staging, risk assessment, therapeutic strategies, therapeutic response and monitoring minimal residual infiltrates of this disease [1–4]. Simultaneous examinations of both marrow smears and sections are mandatory to increase the chance of morphologic detection of discrete metastatic deposits involving the BM. Some authors still accepting, bilateral cytological and histological screening of marrow as the gold standard for initial staging of NB patients. However, the possibility of random patchy distribution of NB infiltrates cannot be excluded, especially during or after therapy, with subsequent possibility of resulting errors [5]. Nowadays, the use of Immunohistochemical (IHC) staining provides considerably higher detection sensitivity with additional prognostic information for NB patients [6]. Mean-while, with the advent of ''Tc-99m'' bone scan (BS), it was shown that many bone metastases may be missed by plain X-rays and that's why skeletal scintigraphy became the procedure of choice to assess bone metastases in different malignancies including NB [7]. Detection of NB deposits has been facilitated by the development and application of the radiopharmaceutical metaiodobenzylguanidine (MIBG) labeled with I-131 or I-123, which localizes in both primary and secondary deposits of NB [8]. Controversy persists as to the need for both MIBG and BS in routine evaluation of NB. Some authors suggested that BS is necessary to fully assess bone involvement at diagnosis but MIBG scan is more suitable for monitoring response to therapy [9,10]. In planning diagnostic or follow-up investigational strategies, NB metastatic deposits in bone and/or BM should be detected as early as possible. Therefore, all investigational detection tools should be conducted simultaneously for precise staging. However, because of the financial conditions in our developing countries and in view of the cost/benefit relationship, the question is, can one detection tool only become satisfactory and replaces others; especially no priorities were specified in the literature according to de novo or follow-up NB cases? The purpose of this study is to compare simultaneous results of nuclear medicine imaging modalities (bone and MIBG scans) versus bilateral BM biopsies (confirmed by immunohistochemical (IHC) staining); in detecting bone and/or BM metastatic deposits in NB patients.

Material and methods

In the period from March 2007 to September 2009, all diagnosed NB cases that were sent, within a week, for staging to the Clinical Pathology department and Nuclear Medicine Unit in the National Cancer Institute, Egypt, were included in this study. Patients recruited were at different points of their clinical courses. Studied cases were 138; of which 46 cases (20 males and 26 females with a median age of 3 years ranging from 4 months to 16 years) were newly diagnosed patients and were grouped as ''De novo cases'', while 92 cases (44 males and 48 females with a median age of 4.5 years ranging from 2 to 17 years) were patients under follow-up and were grouped as ''Follow-up cases''. The cases were subjected to (1) examination of bilateral BM smears and sections, (2) confirmatory IHC staining using Neuron Specific Enolase (NSE) McAb, (3) routine Tc-99m methylene diphosphonate (Tc-99m MDP) bone scan, and (4) 57/138 cases were, in addition, subjected to I-131 MIBG scan. The 57 cases included 15 of the 46 ''De novo cases'' and 42 of the 92 ''Follow-up cases''. All NB diagnostic criteria including characteristic clinical data, pathological details, biochemical findings (e.g. NSE, Ferritin, VMA, and HVA) and expected molecular abnormalities (e.g. N-myc) were verified but not formally mentioned as they were considered outside the scope of this work.

Bone marrow samples preparation and staining

Bilateral BM biopsies and aspirations were subsequently obtained from each case. At least 10, Leishman's stained marrow