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CASE REPORT

A CASE REPORT OF AGGRESSIVE ADULT NEUROBLASTOMA MIMICKING ACUTE LEUKEMIA WITH FULMINANT COURSE AND FATAL OUTCOME

Panovska-Stavridis I.,[1] Ivanovski M.,[1] Hadzi-Pecova L.,[1] Ljatifi A.,[1] Trajkov D.,[2] Spiroski M.,[2] Cevreska L.,[1]

[1]Clinic of Hematology, Faculty of Medicine, Ss. Ciril and Methodius University, Skopje, R. Macedonia
[2]Institute of Immunobiology and Human Genetics, Faculty of Medicine, Ss. Ciril and Methodius University, Skopje, R. Macedonia

A b s t r a c t: A case of aggressive adult neuroblastoma mimicking acute leukemia with fulminant course and fatal outcome is described. Pancytopenia and circulating blasts cells at presentation suggested the diagnosis of acute leukemia in the previously healthy 38 years old Caucasian male patient, but flow-cytometry analysis of the bone marrow disclosed the correct diagnosis of neuroblastoma. The immunophenotype was CD45-/CD56+/CD9+ in around 50% of the mononuclear cells, indicating neuroectodermal origin of the malignant cells. Subsequently, the diagnosis was confirmed by immunohistochemical staining of a bone marrow biopsy.

A review of the reported cases of neuroblastoma with leukemic features showed that several of them were misdiagnosed as having leukemia and that the diagnosis of neuroblastoma was made at autopsy examination, indicating that misdiagnosis may happen more often than is appreciated.

It is in our opinion that the diagnosis of neuroblastoma should be considered in all cases of acute leukemia and pancytopenia, regardless of the age group of the patients.

Key words: neuroblastoma; immunophenotype; acute leukemia; CD56.

Introduction

Neuroblastoma is an embryonic neoplasm of the sympathetic nervous system derived from the primitive neural crest cells and is the most common

extracranial malignant tumor of childhood [1–3]. Forty percent of patients who present with clinical symptoms at diagnosis are under 1 year of age, and less than 5% with clinical symptoms are over the age of 10 [4–5].

Up until June 2008, no more than 65 neuroblastomas in adults (defined as 20 years of age and older) had been reported in the literature [6–12]. Clinical data on survival outcomes of adult patients with neuroblastoma and available information on the influence of the stage, biological features and histopathology to their prognosis are scarce due to the rarity of the disease [12–18]. The majority of the reports describe more chronic course of the disease, but with poorer survival among adults, when compared to those observed in children. Neuroblastoma in adults has some clinical and biological peculiarities and features that are different from those observed in children [6–18]. Adults frequently manifest with an advanced stage of the disease (nearly 90% of cases), despite the more indolent course of the disease in this age group, have a low excretion of the urinary cathecolamine and in the majority of the cases fatal demise. Also, among adults with stage 4 neuroblastoma, a less frequent involvement of the bone marrow and a greater frequency of uncommon metastatic sites, as lungs and brain, were detected. The most common manifestations of the disease in this age group are the result of a tumor mass, most likely an abdominal mass, or a bone pain due to metastases [6–18].

Furthermore, small single institution reports have described poorer long-term prognosis regardless of stage and site for adults than pediatric patients, when treated with standard doses of chemotherapy. High-dose chemotherapy and surgery have been shown to achieve better results in more than 50% of these patients. Other modalities, such as local radiation therapy and the use of agents with confirmed activity, may improve the poor prognosis [19].

Case report

We report a case of aggressive adult neuroblastoma, which presented clinically as acute leukemia but was correctly diagnosed after the flow-cytometry work-up of the bone marrow.

The patient, a previously healthy 38 years old Caucasian male, was admitted to our department with a 4 months history of hip pain, headaches, malaise, weakness, poor appetite and weight loss. On admission, he complained of high fever, persistent diarrhea, abdominal fullness and discomfort, intermittently rapid heartbeat and intensive leg pain that made him unable to walk. The pain developed gradually, first being localized in both feet and lower parts of the legs, with no signs of any trauma, than progressing to involve the whole limbs, spreading upwards from the mid-back area to the cervical spine.

On physical examination, the patient had normal vital signs, was febrile, prostrated and bed-bound. He was well developed but under nourished and pale without hemoragical syndrome. There was no lymphadenopathy. His abdomen was distended, but with present peristalsis. The liver and spleen were 3 cm and 5 cm below the costal margins respectively. No abdominal mass was palpable. Neurological examination showed a right Horner's syndrome (ptosis, miosis and anhidrosis), reduction of the superficial sensitivity on the Th1 and Th2 level and a loss of tendon-muscle reflexes of the lower limbs. He had paraplegia, indicating a possible spinal cord compression. The complete blood counts on admission were: hemoglobin 9.5g/dl, red blood counts $3.26 \times 10^6/\mu l$, hematocrit 28.5%, white blood counts $3.1 \times 10^3/\mu l$ with the following differential counts : 33% lymphocytes, 52% neutrophils, 2% metamyelocytes, 2% erythroblasts and 11% peculiar blastoid cells. The platelets counts were $43 \times 10^3/\mu l$, LDH was 3552U/l.

Acute leukemia was suspected and a bone marrow aspirate and biopsy were performed [20].

Bone marrow morphology analyzed by microscopic examination on May Gruenwald Giemza stained air-dried bone marrow smears revealed infiltration in more than 50% of the bone marrow with atypical "blast" cells [20]. Blast cells showed marked pleomorphisam and hyperchromasia, had round or oval nuclei with scanty to moderate basophilic cytoplasm. The nuclear chromatin was stippled and usually had one small visible nucleolus. The cells were arranged in clusters of varying sizes and some of them formed pseudo-rosettes, as presented at Figure 1.

In rear areas of the bone marrow, morphologically normal, but reduced in number megakaryocytes were present. Suppressed, but normal erythropoesis and myelopoesis were also present.

Cytochemical analysis of the malignant cell did not established lineage involvement.. Staining for myloperoxidase (MPO), non specific esterase (EST) and periodic acid-Schiff (PAS) was negative [20].

Multi parameter immunophenotyping of the bone marrow mononuclear cells did not establish neither lymphoid nor myeloid lineage in the blast cells and indicated involvement of the bone marrow with nonhematopoietic malignancy. In around 50% of the mononuclear cells the immunophenotype was as follows CD45-/CD56+/CD9+, which indicated neuroectodermal origin of the malignant cells and the diagnosis of neuroblastoma was suspected [20–22]. Some of charts with the results from immmunophenotyping are presented at Figure 2.

A **B**

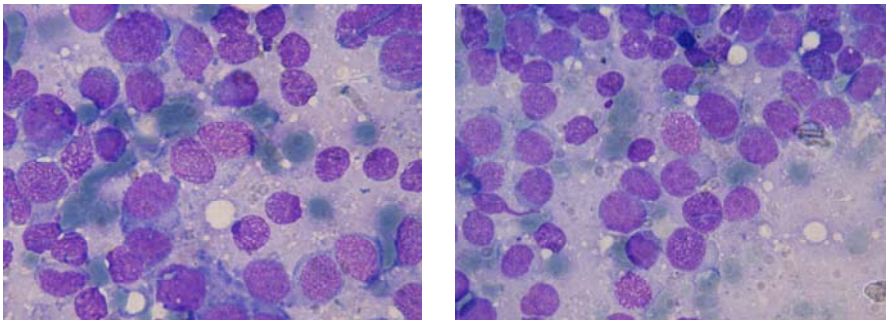

Figure1 – May Gruenwald Giemza stained bone marrow smear: blast cells showing marked pleomorphisam and hyperchromasia with scanty cytoplasm and hyperchromatic nuclei (stippled chromatin and with one or more small visible nucleolus) (A) and some of the malignant cells were forming pseudo-rosettes (B)
Слика 1 – Препарати од периферна крв обоени според методата на May Gruenwald Giemza: плеоморфни бласти клетки со назначена хиперхромазија, скудна цитоплазма и хиперхроматински јадра со неколку видливи јадренца (А). (В) Дел од малигните клетки формираа псевдорозети

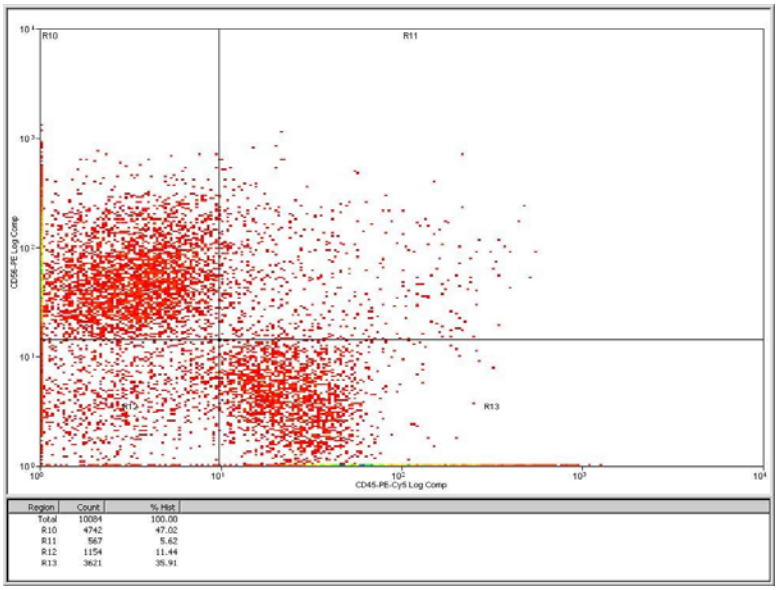

Figure 2 – Charts from the multiparameter flow-cytometry
Слика 2 – Приказ од анализите со проточен цитометар

A routine second opinion by a reference pathologist was also interpreted as neuroblastoma and confirmed with positive immunohistochemical staining for neuron-specific enolase (NSE), chromogranin, synaptophysin and MIC2 gene and negative for LCA as illustrated on Figure 3 [22].

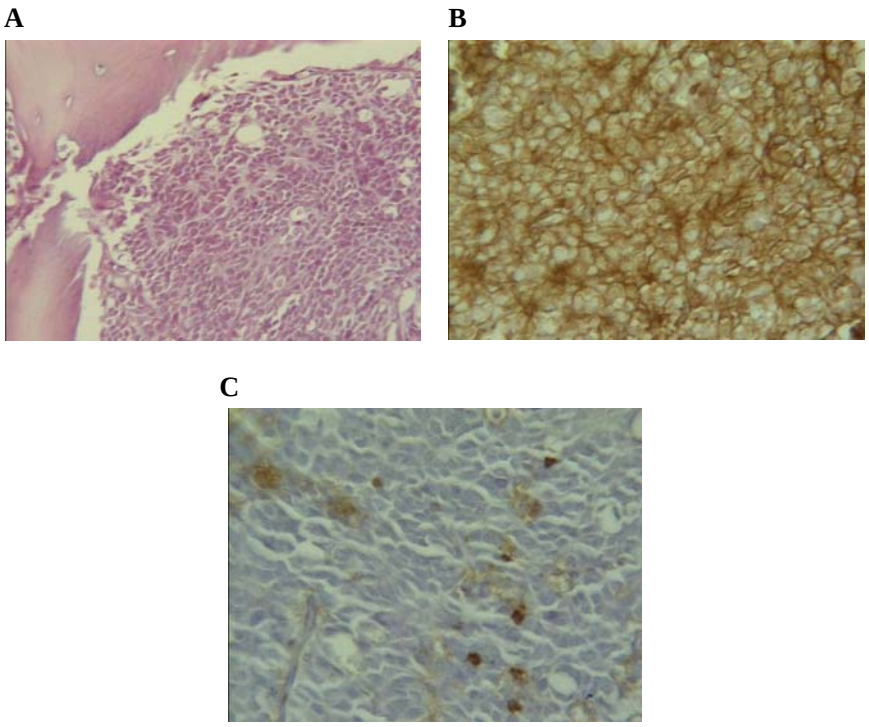

Figure 3 – Paraffin sections of bone marrow stained with Hemalaun-eozin (A), positive immunohistochemistry staining for MIC2 geneexpression (B) and negative immunohistochemistry staining for LCA expression (C)
Слика 3 – Имунохистолошки препарати од коскената срцевина (А) обоени со Hemalaun-eozin, позитивна експресија на MIC2 ген (В) и негативна експресија за LCA (С)

A work-up for neuroblastoma was done [23]. Homovanillic acid and vaillylmandellic acid were found to be elevated. Imaging studies were indicated. A CT scan of the chest and abdomen showed bilateral pleural effusion without metastatic lung involvement. The spleen and liver were extremely enlarged without defects and the patient also had distended bowels. A spinal MRI sho-

wed multiple osteolitic lesions on the spinal vertebrae, compressive fracture at Th2 level and a paraspinal tumor mass that extended through the intervertebral foramina and compressed the spinal cord, as presented at Figure 4.

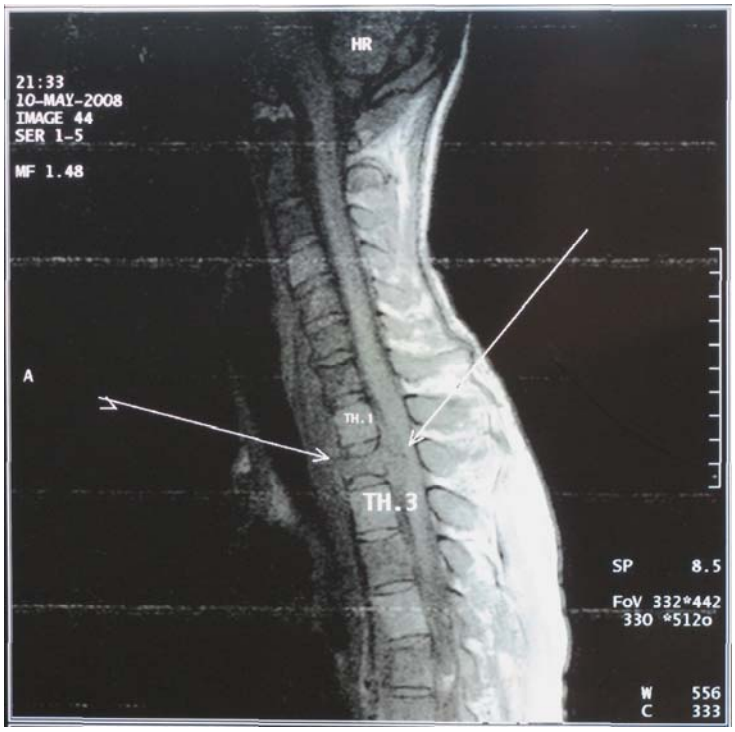

Figure 4 – Spinal MRI
Слика 4 – Магнентна резонанца на 'рбетниот столб

The investigations showed that the patient had a disseminated neuroblastoma, stage 4 according to the International Neuroblastoma Staging System [14, 15]. Treatment with an intensive chemotherapy regimen that is used in high-risk neuroblastomas was initiated. The patient received the first cycle of therapy with cisplatin (60mg per square meter of body surface area) on day 0, doxorubicin 30mg/m^2 on day 2, etoposide 100mg/m^2 on days 2 and 5 and cyclophosphamide 1000mg/m^2 on days 3 and 4. Local radiotherapy for spinal cord decompression was planned after the completion of the first cycle of chemotherapy, in order to prevent the development of permanent neurological impairment. Unfortunately, the patient failed to improve and died as a result of cerebral bleeding nine days after treatment initiation. Autopsy was not performed.

Discussion

Several groups have reported cases of neuroblastoma that were initially misdiagnosed as acute leukemia [24–32]. Symptoms in our patient and others usually include pain, hepatomegaly and problems related to pancytopenia which can be common to both neurobastoma and leukemia. However, in majority of those cases neuroblastoma was diagnosed postmortem, at autopsy examination. Only one of illustrated cases is in an adult, with initial symptoms and findings that suggested idiopathic thrombocytopenic purpura and later developed a clinic picture of acute leukemia. In this case autopsy disclosed the correct diagnosis [25]. A case of neuroblastoma in adult presented as acute leukemia and correctly diagnosed at presentation is never reported. We now report, to our knowledge the first case of aggressive adult neuroblastoma presented as acute leukemia but correctly diagnosed after the initial flow-cytometry analysis of the bone marrow.

Immunophenotyping is essential in the diagnosis of acute leukemias, demonstrates a particular lineage involvement, has biologic and prognostic significance and is one of the mayor tools for their classification.

Our patient had pancytopenia and circulating malignant cells at diagnosis and underwent the standard routine evaluation for acute leukemia. Morphology and cytochemistry couldn't established lineage involvement in this case. Further analyses by a triple-color flow-cytometry assay, based on CD45 gating strategy indicated involvement of the bone marrow with nonhematopoietic malignancy. Immunophenotype of the malignant cells was CD45-/CD56+/CD9+ and indicated neuroectodermal origin of the tumor cells and though, very unusual and rare for the patients age, the diagnosis of neuroblastoma was suspected [20–22].

Approximately 40% of pediatrics patient with neuroblastoma at presentation have high risk stage 4 diseases with bone marrow involvement. Extensive bone marrow metastasis in these patients usually results in pancytopenia [22, 34].

A multi-color flow cytometric assays using different combination of a CD9, CD81, CD56 and CD45 monoclonal antibodies are established as sensitive and specific methods for detecting occult neuroblastoma cells in peripheral blood and bone marrow [21, 22].

CD56 antigen presents as an isoform of the neural adhesion molecules which is invariably and constantly expressed on neuroblastoma cells. Initially was described as a marker of natural killer cell and afterward its usefulness has been recognized in the diagnosis of several lympho-hematopoietic neoplasm including myelomas, myeloid leukemias and in many other malignant tumors such as neuroendocrine tumors.

A review of the reported cases of neuroblastoma with leukemic features showed that several of them were misdiagnosed as having leukemia, and the diagnosis of neuroblastoma was made at autopsy examination, suggesting that this may happen more often than is appreciated.

Although, the scattered reports in the literature illustrate a less frequent involvement of the bone marrow among adults with stage 4 neuroblastoma [7], it is in our opinion that neuroblastoma should be reconsidered in the differential diagnosis in all cases of acute leukemia and pancytopenia, regardless of the age group of the patients.

We suggest CD56 monoclonal antibody to be included in the primary flow-cytometry acute leukemia assays, as initial screening tool for recognizing cases of neuroblastoma which simulate acute leukemia [33].

These diagnostic approaches will further improve the individual risk stratification of the patients at diagnosis and will smooth the progress of correct therapy decision.

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Резиме

ПРИКАЗ НА СЛУЧАЈ НА АГРЕСИВЕН АДОЛТЕН НЕУРОБЛАСТОМ ПРЕЗЕНТИРАН КАКО АКУТНА ЛЕУКЕМИЈА СО ФУЛМИНАНТЕН ТЕК И ФАТАЛЕН КРАЈ НА БОЛЕСТА

Пановска-Ставридис И.,[1] Ивановски М.,[1] Хаџи-Пецова Л.,[1] Љатифи А.,[1] Трајков Д.,[2] Спироски М.,[2] Чевреска Л.[1]

[1]Клиника за хематологија, Медицински факултет, Универзитет Св. Кирил и Методиј, Скопје, Р. Македонија

[2] Институт за имунологија и хумана генетика, Медицински факултет, Универзитет Св. Кирил и Методиј, Скопје, Р. Македонија

Во нашата студија е презентиран случај на агресивен адолтен неуробластом со клиничка слика на акутна леукемија, фулминантен тек и фатален крај на болеста. Кај претходно здравиот 38-годишен бел маж, иницијалната панцитопенија и циркулирачките малигни клетки индицираа акутна леукемија, но преку анализите со проточен цитометар беше поставена прецизна дијагноза на неуробластом. Околу 50% од мононуклеарните клетки го имаа имунофенотипот CD45-/CD56+/CD9+ кој е во прилог на тумор од неуро-

ектодермално потекло. Дијагнозата беше потврдена со имунохистохемиски анализи на примерок од коскена биопсија.

Анализата на податоците од литературата за неуробластоми со карактеристики на акутна леукемија покажа дека најголем број од нив се дијагностицирани со обдукција, што укажува дека овие случаи најчесто остануваат недијагностицирани.

Наш заклучок е дека дијагнозата на неуробластом треба да се разгледа диференцијално дијагностички кај секој случај на панцитопенија и/или акутна леукемија, независно од возраста на пациентите.

Клучни зборови: неуробластом; имунофенотип; акутна леукемија; CD56.

Corresponding Author:

Irina Panovska-Stavridis, MD
Clinic of Hematology, Faculty of Medicine,
University *Ss. Cyril and Methodius* Skopje,
Republic of Macedonia
Tel.: +389 2 3147 782
Fax: +389 2 393 610
Mobile phone: +389 70 221 089

E-mail: dr_irina@yahoo.com