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Case Report

Metastatic neuroblastoma presenting without a primary tumor: A case report ☆,☆☆,★

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ABSTRACT

Neuroblastoma is the most common extracranial, intrabdominal, suprarenal solid tumor of childhood. It usually presents with painless abdominal mass with or without abdominal pain. We report an unusual subtle cervical lymph nodes enlargement associated with fever and joint pain. Neuroblastoma usually starts in the adrenal glands. What is unique in our case is that the presentation is without a primary tumor. We present a case of 4-year-old female Egyptian complaining of recurrent pattern of fever and generalized joint pain, with lower neck swelling for 1-month duration. Laboratory investigations revealed a normochromic normocytic anemia and increased inflammatory markers. Immunohistochemistry staining and immunophenotyping of the cervical lymph nodes and bone marrows confirmed the diagnosis of Neuroblastoma. This case report highlights the importance of recognizing the possibility of a metastatic neuroblastoma without primary tumor in children who presented solely of lymphadenopathy.

Neuroblastoma is the most common extracranial solid tumor of childhood which accounts for up to 15% of all pediatric cancer fatalities [1]. Additionally, it is the most common in the first year of life [2]. Both the manifestations and prognosis of neuroblastoma are highly variable ranging from spontaneous regression to widespread metastasis that is unresponsive to treatment [3]. The most common presentation of neuroblastoma is abdominal mass, the tumor is mostly located in the adrenal gland [4]. The purpose of this paper is to report a case in which the initial presentation of the patient was subtle cer-

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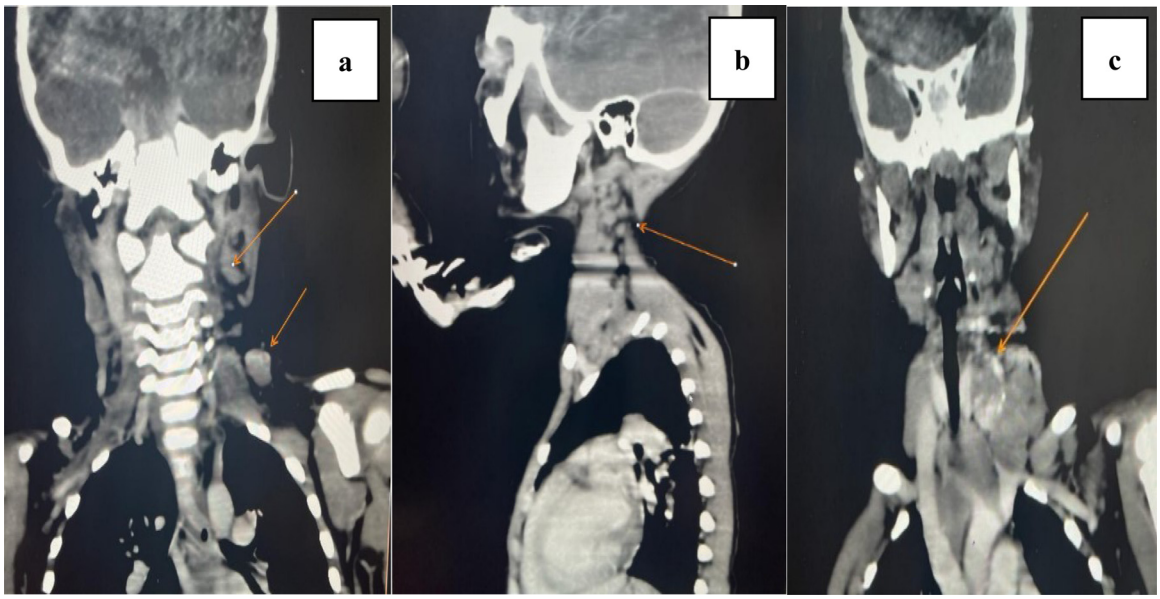

Fig. 1 – Neck CT, (A) coronal and (B) sagittal section, showing multiple, bilaterally enlarged deep cervical lymph nodes seen within group II, III, and IV on the left side and group II-A and B on the right, with the largest appearing matted and showing calcification. (C) Another coronal section, showing lower left cervical amalgamated nodal mass lesions involving groups IV and V-B with the largest (orange arrow) in the former, extending to the root of the neck and supraclavicular region with internal calcifications (Color version of figure is available online).

vical lymphadenopathy associated with recurrent fever and no signs of primary involvement. We aim to shed light on this atypical presentation for a rather common childhood malignancy.

Case presentation

A 4-year-old Egyptian female complaining of recurrent pattern of fever and generalized mild joint pain that started 1 month ago associated with left neck swelling. Her past medical history is unremarkable. No history of loss of weight, loss of appetite, or night sweats. Physical examination revealed left lower neck, mobile, non-tender group of lymph nodes. No hepatosplenomegaly or lymphadenopathy were palpable.

Laboratory studies revealed normochromic, normocytic anemia, and high inflammatory markers erythrocyte sedemntation rate (ESR) 105 mm/s. Ultrasound of the left side of the neck revealed underlying solid macro-lobulated mass lesion, measures about 60 × 22 mm in diameter. The mass shows moderate vascularity inside and marked scattered calcifications.

Unenhanced and contrast-enhanced neck computed tomography (CT) showed multiple enlarged neck group II-IV of left lymph nodes. The largest appear matted with adjacent enlarged nodes and showing calcification, measuring 22 × 18 × 18 mm (Fig. 1A and B). In addition, left lower cervical amalgamated nodal mass lesions, largest measuring 3 × 2.5 cm with internal calcifications was seen (Fig. 1C). Abdominopelvic CT showed liver is enlarged, right hepatic lobe measures 9.5 cm in the mid clavicular line showing multiple hypodense hepatic lesions, the largest seen in segment VI measuring 2.2 × 1.6 cm (Fig. 2C). Spleen is mildly enlarged measuring 7 cm in its bipolar dimension. Adrenal glands, kidneys, pelvic organs, and retroperitoneal are unremarkable.

Biopsies were obtained from the cervical lymph nodes and bone marrow. Bilateral bone marrow aspirations and biopsies showed depressed erythropoiesis and myelopoiesis with sheets of solitary cells of malignant small round blue cells forming rosettes within neurofibrillary matrix of nonhemopoietic origin. The targeted neoplastic cells were strongly positive for Synaptophysin, CD56, Chromogranin, while negative for other markers. Thus, the immunostaining results from the cervical lymph node and bone marrow biopsy is consistent with poorly differentiated metastatic neuroblastoma (Fig. 3A-D).

Discussion

In this case report, we have a 4-year-old female presenting with a number of atypical clinical features and a lack of commonly seen findings with the final diagnosis of metastatic neuroblastoma. Neuroblastoma is a soft tissue tumor arising from derivatives of the neural crest cells. Therefore, the tumor can not only arise in the adrenal glands, but indeed at any point along the sympathetic chain. A study of 8369 children with neuroblastoma revealed the breakdown of primary tumor sites as 47% in the adrenals, 24% in the abdomen/retroperitoneum, 15% in the thoracic cavity, 3% in the

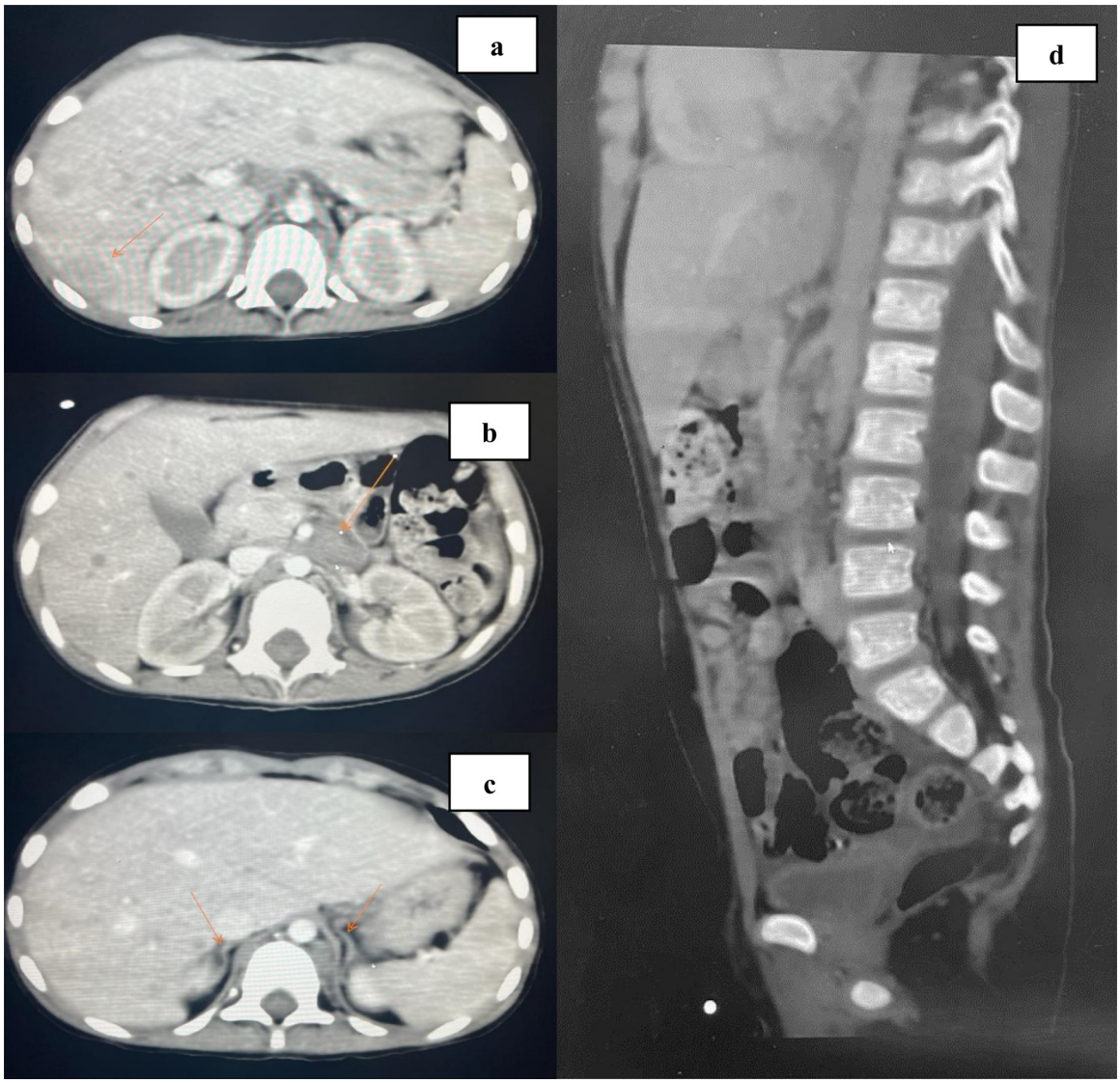

Fig. 2 – (A) Abdominopelvic CT, axial section, showing multiple hepatic hypodense lesions with the largest (orange arrow) seen in the right lobe in segment VI. (B) Abdominopelvic CT, axial section, showing multiple partially amalgamated abdominal lymph nodes involving the pre- and para-aortic groups, with the largest (orange arrow) as shown. (C) Abdominopelvic CT, axial section, showing the unusually normal appearance of the adrenal glands (orange arrows). (D) Abdominopelvic CT, sagittal section, showing a questionable sclerotic appearance of the vertebrae with no definite focal osseous lesions (Color version of figure is available online).

pelvis, 3% in the neck, and 8% within other unspecified primary tumor sites [5]. However, in rare cases, a primary tumor cannot be discerned [6] As such, limited information exists regarding the clinical features of neuroblastomas of unknown primary site. Despite extensive CT evaluation in our case, a primary tumor could not be detected. One study theorizes that this unusual presentation of metastatic neuroblastoma without an apparent primary site may be due to early dissemination from a previous primary tumor followed by the tumor's spontaneous regression or complete maturation [6]. Spontaneous regression, in particular, is a well-described phenomenon in neuroblastomas. Since a primary tumor could not be identified, metastasis to other organs resulted in almost all of the clinical manifestations present in our case, whether local or systemic. Indeed, more than 50% of all neuroblastoma patients have metastatic involvement at the time of diagnosis, frequently in the lymph nodes (typically regional), bone marrow, bone, and liver [7,8]. However, metastasis to these organs in our case also presented atypically as is discussed below.

The vague signs and symptoms of fever of unknown origin, generalized joint pain and bone aches, cervical lymphadenopathy and no palpable masses in our case mimic diseases of infectious etiology; this combination of signs and symptoms is rarely seen in neuroblastoma. Indeed, when the patient presented at a different hospital earlier in the disease course with fever and hip pain, a provisional diagnosis of septic arthritis was made. Studies show that, in a child exhibiting manifestations of fever and hip pain in the presence of unex-

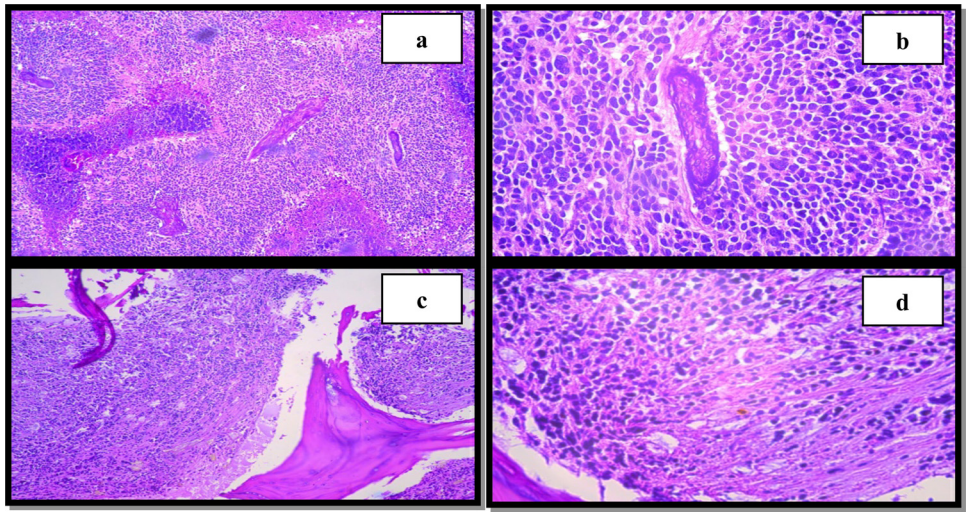

Fig. 3 – (A) Low power view of metastatic poorly differentiated subtypes of neuroblastoma to lymph node with a high mitotic karyorrhectic index (about 20%). (B) High power view of metastatic poorly differentiated neuroblastoma to cervical lymph node. (C) Bone marrow metastatic deposits of poorly differentiated neuroblastoma in the form of para-trabecular nests. (D) High power view of metastatic poorly differentiated neuroblastoma to bone marrow.

plained anemia and a high ESR or in the presence of negative joint fluid cultures and poor response to conventional treatment of septic arthritis, the possibility of malignancy, such as bone metastasis from a neuroblastoma, should also be considered [9,10]. This may have led to an earlier diagnosis in our patient and initiation of appropriate treatment.

Notably, in our case, there was a lack of clinical signs, such as no abdominal distension, no palpable masses, abdominal or otherwise, that would be indicative of a primary tumor and no hepatosplenomegaly despite later CT evaluation showing moderate hepatic enlargement with multiple hypodense lesions and mild splenic enlargement. In particular, cervical lymph node enlargement was unusually one of the only significant and positive findings on physical examination. A retrospective study of 118 patients diagnosed with neuroblastoma revealed 19 that had head and neck involvement secondary to metastatic disease. Of those 19, 18 (95%) had bony craniofacial metastasis while only 1 (5%) had cervical lymph node metastasis [11]. This highlights the rarity of cervical lymphadenopathy in the context of metastatic involvement of the head and neck in neuroblastomas.

An unusual laboratory finding in this case is the lack of pancytopenia despite extensive bone marrow involvement. Bilateral bone marrow examination showed almost total infiltration by sheets and solitary cells of neuroblastoma. A retrospective study analyzing bone marrow infiltration status in neuroblastoma and its relation to hematological parameters identified 63 out of 111 cases with bone marrow infiltration. These cases were subsequently divided into early stage, intermediate stage, and late-stage cases. Findings revealed that intermediate and late-stage cases exhibited a significant reduction in hemoglobin, white blood cell count, and platelet count with a significantly increased incidence of leukopenia, anemia, and thrombocytopenia in these cases [12]. While our late-stage case did exhibit anemia, the white blood cell and platelet count were within normal levels. However, judging from the 2 complete blood counts taken about 1 month apart showing moderate decreases in the aforementioned hematological parameters between them, it is possible that pancytopenia would have developed if the diagnosis was delayed even further. The same study showed significantly higher lactate dehydrogenase (LDH) serum levels in patients with bone marrow involvement compared to without (1192.3 ± 1130.2 U/L vs 487.5 ± 489.5 U/L, retrospectively, $P = .000$) [12]. Despite extensive bone marrow involvement in our case however, serum LDH at the time of diagnosis, while elevated, was comparatively lower at 354 U/L.

Ultimately, this elevated LDH led to the suspicion of a hematopoietic malignancy, such as leukemia or lymphoma. However, subsequent lymph node and bone marrow biopsy histopathology and immunohistochemistry revealed the presence of undifferentiated small-blue-round-cells and Homer Wright rosettes (pseudo-rosettes) staining positive for Synaptophysin, CD56, and Chromogranin which was consistent with metastatic neuroblastoma. Interestingly, while Homer Wright rosettes are seen in only up to 30% of cases, they are a characteristic finding of neuroblastomas [13].

Conclusions

This case report highlights the importance of recognizing the possibility of a metastatic neuroblastoma without primary tumor in children that present with signs and symptoms suggestive of metastatic organ involvement despite there being no masses indicative of the primary tumor on physical examination or by radiology scans. More detailed imaging techniques as well as lymph node or bone marrow biopsy would thus be indicated, especially if clinical suspicion of malig-

nancy is high. Clinicians should also be aware of the diagnostic pitfalls when assessing metastatic neuroblastomas that may lead to a delay in establishing the diagnosis, and hence treatment. The main lesson learned from this case is to keep the doors open for suspecting metastatic tumor even in the absence of a primary origin in the classically known site

Declarations

Ethics approval and consent to participate is done. All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was obtained from the Pediatrics Department, Saudi German Hospital, Jeddah, and Saudi Arabia.

Patient consent

The treating physician of the patient, Dr Abdulla Baothman, has obtained consent from the patient's parents for publication of the case. No images that lead to the identification of the patient identify have been used in this case report. All images used are checked for patient confidentiality and we ensured no identifiable features as patients details are included. Consent for publication has been obtained from the child's parents for the publication of this case report.

Availability of data and material

The datasets used during the current study are available by the corresponding author in reasonable request.

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