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Prevalence of Secondary Bone Marrow Tumors in Pediatric Patients and Association with Clinical and Hematological Parameters

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Abstract

Introduction. The clinical and histopathological signs of bone marrow involvement by solid tumors may overlap with hematological neoplasms which can pose a diagnostic challenge.
Purpose. To describe bone marrow morphology when involved with solid pediatric tumors and find the association with clinical presentation and blood indices derangements.
Materials and methods. Bone marrow aspirates and biopsies of a total of 65 patients with solid tumors were retrospectively evaluated during the period between Jan 2020 to Mar 2021. Clinical and complete blood count were retrieved form patients notes.
Results. The patients mean age was 4.0±2.8 years. Male to female ratio was 1.4: 1. 24.6% of patients in our cohort has bone marrow involvement as a presenting feature. Fifty-two (80%) of solid tumor that involved the bone marrow were neuroblastoma followed by retinoblastoma 5 (7.7%). The dominant bone marrow morphology observed in all aspirate and biopsy was non homoeotic primitive mononuclear aggregates and discrete cells. Fibroblastic reaction and Neurofibrillary matrix were observed in 14 (21.5%) and 2 (3.1%) respectively. In addition to anemia, leukopenia was reported in 18 (27.7%), thrombocytopenia in 13 (20%) and thrombocytosis in 10 (15.4%) of these patients. Bone marrow failure and pancytopenia was reported in 5 (7.7%) of the cases, 80% of them had neuroblastoma, the rest had rhabdomyosarcoma.

Conclusion. Bone marrow metastasis in pediatrics with nonspecific symptoms represent a diagnosis challenge that can be resolved by bone marrow biopsy. Neuroblastoma was the most often occurring solid tumor in Iraqi children that metastasized to the bone marrow.
Keywords: solid tumors, pediatrics tumors, bone marrow metastasis, homoeotic primitive mononuclear, bone marrow

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Распространенность вторичных опухолей костного мозга у пациентов детского возраста и их взаимосвязь с клиническими и гематологическими показателями

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Резюме

Введение. Клинические и гистопатологические признаки поражения костного мозга солидными опухолями могут сочетаться с гематологическими новообразованиями, что вызывает трудности при постановке диагноза.
Цель. Описать морфологические особенности костного мозга у педиатрических пациентов с солидными опухолями и установить взаимосвязь между клиническими проявлениями и отклонениями в показателях крови.
Материалы и методы. Аспираты и биоптаты костного мозга 65 пациентов с солидными опухолями исследовали ретроспективно в период с января 2020 по март 2021 г. Клинические данные и показатели общего анализа крови были получены из карточек пациентов.

Результаты. Средний возраст пациентов составил 4,0±2,8 года. Соотношение мальчиков и девочек – 1,4 : 1. У 24,6% пациентов исследуемой когорты поражение костного мозга было основным признаком. 52 (80%) солидные опухоли, вызвавшие поражение костного мозга, были представлены нейробластомами, следующими по частоте встречаемости были ретинобластомы (5 (7,7%)). Преобладающим морфологическим признаком, наблюдаемым во всех аспиратах и биоптатах костного мозга, было наличие негомеотических примитивных мононуклеарных агрегатов и дискретных клеток. Фибробластическая реакция и нейрофибриллярный матрикс были отмечены в 14 (21,5%) и 2 (3,1%) случаях соответственно. Помимо анемии, у 18 (27,7%) пациентов наблюдалась лейкопения, у 13 (20%) – тромбоцитопения, у 10 (15,4%) – тромбоцитоз. Костномозговая недостаточность и панцитопения были обнаружены в 5 (7,7%) случаях, причем у 80% пациентов были выявлены нейробластомы, а у остальных – рабдомиосаркомы.
Заключение. У педиатрических пациентов с неспецифическими симптомами метастазы в костный мозг представляют собой диагностическую проблему, которую можно преодолеть с помощью биопсии костного мозга. У иракских детей наиболее часто встречающейся солидной опухолью, дающей метастазы в костный мозг, была нейробластома.
Ключевые слова: солидные опухоли, опухоли у детей, метастазы в костный мозг, гомеотические первичные мононуклеары, костный мозг

■ INTRODUCTION

Pediatric solid tumors are a heterogeneous group of diseases account for more than 60% of all childhood malignancies. The spectrum of solid tumors found in children differs considerably from that found in adults [1]. Pediatric neoplasms encompass a variety of tumor types, including central nervous system (CNS) tumors accounting for 35% of cases, neuroblastoma comprising 15% of cases, soft tissue sarcomas such as rhabdomyosarcoma accounting for 7% of cases, Wilms tumor accounting for 6% of cases, bone tumors including osteosarcoma and Ewing sarcoma accounting for 8% of cases, retinoblastoma accounting for 5% of cases, and miscellaneous tumors such as hepatoblastoma accounting for 17% of cases [2]. The past five decades have witnessed a notable enhancement in the rate of remission among pediatric patients with solid tumors. This improvement can be attributed to a deeper comprehension of the biological and clinical dimensions of these tumors, which has facilitated the refinement of clinical staging systems. Additionally, the consistent implementation of supportive care measures has played a crucial role in this progress. Furthermore, the development of more effective treatment strategies, involving the integration of chemotherapy, surgery, and radiation therapy, has contributed significantly to the observed advancements [1]. The incidence of pediatric cancer, including hematological cancers, in Iraq exhibited a consistent stability, with rates ranging from 9.55 to 9.92 per 100,000 children, over the period of 2000 to 2016. Childhood cancer in Iraq comprises approximately 7.5–8.5% of all cancer cases, with an annual average of 1000 cases [3]. The prevalence of the disease aligns with the worldwide average of 10 cases per 100,000 individuals, as well as specific regional rates observed in Jordan (9.9 cases per 100,000) [4] and Iran (17.5 cases per 100,000) [5], However, it is

important to note that the disease continues to impose a significant burden due to its elevated fatality rate. In developing countries, the mortality rate can reach as high as 98%, while in developed countries, it can be as low as 15% [6].

The bone is a common site of metastases for solid tumors [7]. The unique bone microenvironment which has rich vascular supply and chemo attractive factors produced by stromal cells, osteoblasts, osteoclasts, and osteocytes provides an ideal niche for tumor cell attachment and proliferation [8]. Bone metastasis is frequent in children suffering from neuroblastoma [8], osteosarcoma [9] and Ewing sarcoma [10, 11]. For instance, Taguchi and colleagues reported that bone metastasis in neuroblastoma affected the skull in 61.4%, femur in 56.8%, orbit in 27.3% and spine in 22.7% [12]. The presence of bone metastases is a negative prognostic indicator. The aforementioned phenomenon has a detrimental impact on the overall well-being of individuals, leading to a decline in their quality of life and an escalation in both morbidity and mortality rates [11]. Around 70% of individuals diagnosed with neuroblastoma exhibit metastatic spread at the time of diagnosis. The metastasis often occurs in the bone and bone marrow, which is indicative of a highly aggressive tumor and an unfavorable prognosis, even with intensive chemotherapy and autologous hematopoietic stem-cell transplantation [13].

Diagnoses of bone marrow involvement by non-hematological malignancies are made using BM biopsy, cytological and histological studies of the bone. The study of bone marrow not only enables the identification of metastatic cells' lodgement, invasion, and extravascular dissemination at the cellular level, but also provides information about the host marrow's responses. Metastatic tumor detection in the bone marrow is critical for clinical staging, determining therapy response, and determining overall survival [14].

The clinical and histopathological signs of bone marrow involvement by solid tumors may overlap with hematological neoplasms which are relatively frequent in this age group. This can pose a diagnostic challenge, especially if it is the initial presenting symptom. In this study we presented a series of solid pediatric tumors with bone metastasis, describing BM morphology for each tumor and associated clinical presentation and blood indices derangements.

■ PURPOSE OF THE STUDY

To describe bone marrow morphology when involved with solid pediatric tumors and find the association with clinical presentation and blood indices derangements.

■ MATERIALS AND METHODS

Bone marrow aspirates and biopsies of a total of 65 patients with solid tumors were retrospectively evaluated during the period between Jan 2020 to Mar 2021 in Children Welfare Teaching Hospital in Bagdad. Patient's demographics and clinical presentation were retrieved form achieved patients notes.

Children under the age of 12 with a newly diagnosed solid tumor of with bone marrow metastasis with or without a localized tissue tumor, were eligible for inclusion. Patients who had previously had or were currently receiving treatment were excluded.

A Jamshidi aspiration and trephine needles were used to obtain bone marrow aspirates and biopsies from the posterior iliac crest. Five methanol-fixed smears were stained with Leishman's stain. A 1.5 cm core was taken and processed at the histopathology laboratory and sections 3–4 μm thick sections were stained with Hematoxylin and eosin were used

to stain (H&E) and immunohistochemical (IHC) panel. Peripheral blood cell morphology was evaluated using Leishman's-stained smears were examined under light microscope.

For each patient, 3 ml venous blood sample was collected in EDTA tube and complete blood count was obtained using an automated electronic counter (Beckman Coulter, ACT. 5 diff. USA).

The Statistical Package for Social Sciences software for windows version 25 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. Observational data was presented in the form of frequencies and percentages. According to the data distribution, continuous variables were expressed as mean, standard deviation (SD), or range. To assess the proportions of nominal/ordinal variables in different groups, statistical comparisons were performed using the Chi-square test or Fisher's exact tests, as appropriate. Statistical significance was defined as a P value less than 0.05.

■ RESULTS

The mean age of patients was 4.0±2.8 years ranging between 5 months – 12 years. The majority (73.8%) were younger than 5 years. Male to female ratio was 1.4: 1. Fifty-two (80%) of solid tumor that involved the bone marrow were neuroblastoma followed by retinoblastoma 5 (7.7%) as further detailed in Table 1. Bone marrow involvement at the first diagnosis was reported in 11 (21.2%) of neuroblastoma patients.

The most frequent presenting features of these patients was abdominal mass or distention 36 (55.3%) (Fig. 1).

This was seen in 57.7% of neuroblastoma patients, 60% of retinoblastoma, 66.7% of PNET and 50% of rhabdomyosarcoma (Table 2).

Ocular manifestations were observed in 23.1% of the patients distributed between neuroblastoma, retinoblastoma and rhabdomyosarcoma. Nonspecific symptoms such as fever, weight loss and bone pain were reported by 16 (24.6%) of the cases, 11 (68.7%) turned to be retinoblastoma and 3 (18.8%) were Ewing sarcoma.

The dominant bone marrow morphology observed in all aspirate and biopsy of this cohort was non homoeotic primitive mononuclear aggregates. Additionally, discrete

Table 1
Patients demographics

Parameter	Frequency	Percentage
Age		
<5	48	73.8
5–9	10	15.4
≥10	7	10.8
Gender		
Male	38	58.5
Female	27	41.5
Type of the tumor		
Neuroblastoma	52	80
Retinoblastoma	5	7.7
Ewing	3	4.6
Primitive neuroectodermal tumour	3	4.6
Rhabdomyosarcoma	2	3.1

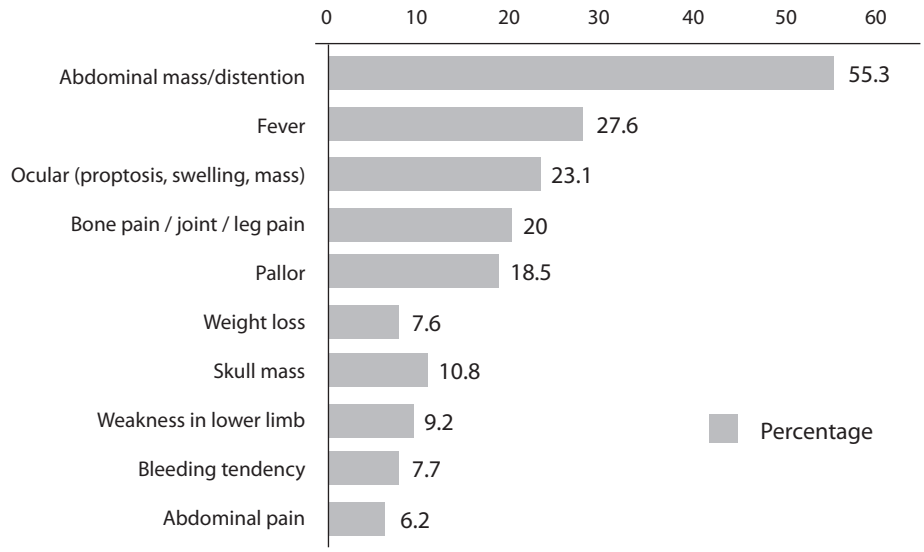

Fig. 1. Clinical presentation of patients with solid tumor infiltrating bone marrow

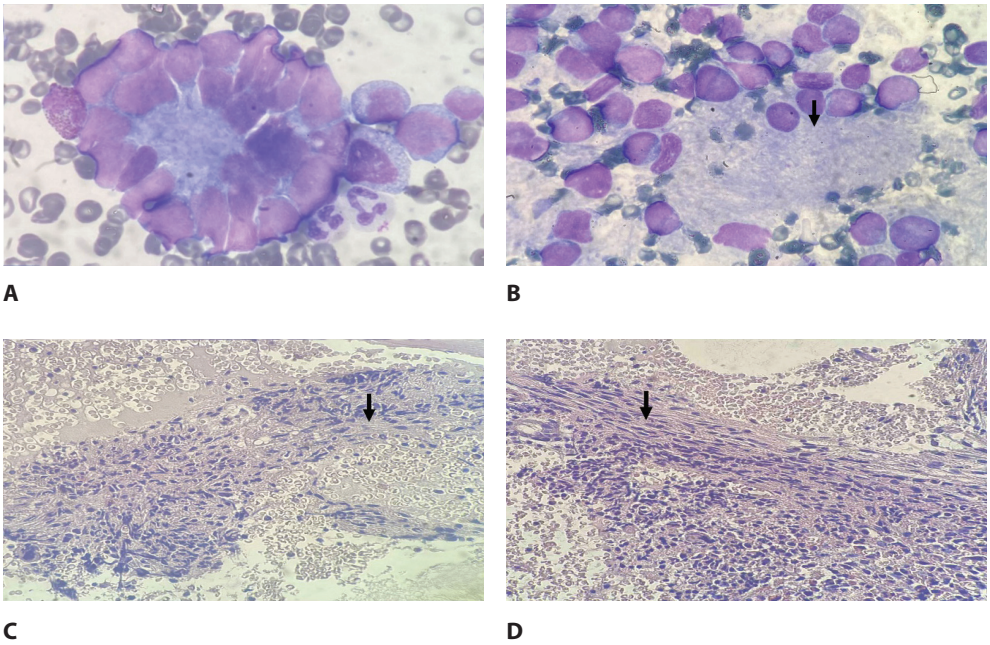

Fig. 2. Micrographs of bone marrow aspiration and biopsy. A – Bone marrow aspirate showing a cohesive cluster of neoplastic cells forming a Rosette; B – Bone marrow aspirate showing diffuse infiltration of malignant non hemopoietic elements with intermingled neurofibrillary components (arrow); Lishman stain, magnification 400x. C, D – Bone marrow biopsies showing disturbed architecture due to heavy infiltration by non-hemopoietic elements malignant mononuclear with fibroblastic reaction (arrows), H&E, magnification 200X

Table 2
Patients characteristics, bone marrow morphology and peripheral blood indices in different tumor types

Tumor type	No. (%)	Age Mean ±SD	Male no (%) female no (%)	Clinical feature No. (%)	Bone marrow morphology No. (%)	IHC	Hb Mean± SD	WBC count Mean±SD	Platelet count Mean± SD
Neuroblastoma	52 (80)	3.8 (2.6)	M: 32 (61.5) F: 20 (38.5)	Abdominal mass 30 (57.7) Fever 16 (30.8) Weight loss 5 (9.6) Bone/joint swelling, pain 9 (17.3) Limb weakness 6 (11.5) Abdominal pain 4 (7.7) Pallor 9 (17.3) Bleeding tendency 1 (1.9) Ocular signs 9 (17.3) Skull mass 5 (9.6) Others 8 (15.4)	Non-hemopoietic primitive mononuclear aggregates 52 (100) Discrete cells 34 (65.4) Fibroblastic reaction 13 (25) Neuro-fibrillar 2 (3.8)	Chromogranin (+) , Synaptophysin (+), CD56 (+), CD99 (-) Myogenin (-)	8.4 (1.9)	19.7 (8.8)	270 (164.2)
Retinoblastoma	5 (7.7)	3.5 (0.5)	M: 1 (20) F: 4 (80)	Abdominal mass 3 (60) Ocular/orbital signs 4 (80)	Non-hemopoietic primitive mononuclear aggregates 5 (100) Discrete cells 4 (80) Fibroblastic reaction 1 (20) Neuro-fibrillar 0	NSE (+), synaptophysin (+), CD99 (-)	10.4 (1.1)	10.2 (2.6)	241 (90.2)
Ewing sarcoma	3 (4.6)	5.167 (3.3)	M: 2 (66.7) F: 1 (33.3)	Bone/joint swelling or pain 3 (100)	Non-hemopoietic primitive mononuclear aggregates 3 (100) Discrete cells 2 (66.7) Fibroblastic reaction 0 Neuro-fibrillar 0	CD99 (+), NSE (+), Desmin (-)	11.5 (1.9)	8.1 (2.3)	305 (83.7)
Primitive neuro-ectodermal tumor	3 (4.6)	6.2 (5.1)	M: 3 (100)	Abdominal mass 2 (66.7) Bone/joint swelling, pain 1 (33.3) lower back mass 1 (33.3)	Non-hemopoietic primitive mononuclear aggregates 3(100) Discrete cells 2 (66.7) Fibroblastic reaction 0 Neuro-fibrillar 0	CD99 (+), NSE (+), Desmin (-)	10.1 (2.2)	13.1 (9.9)	400 (188.9)
Rhabdo-myosarcoma	2 (3.1)	6.3 (5.1)	F: 2 (100)	Abdominal mass 1 (50) Fever 2 (100) Bleeding tendency 1 (50) Ocular /orbital signs 1(50)	Non-hemopoietic primitive mononuclear aggregates 2 (100) Discrete cells 2 (100)	Myogenin (+), CD99 (-), NSE (-)	6.5 (5.5)	7.1 (5.4)	124.5 (129)

Table 3
Hematological profile of study group

Peripheral blood	Frequency	Percentage
Anemia	58	89.2
Leukopenia	18	27.7
Leukocytosis	4	6.1
Thrombocytopenia	13	20
Thrombocytosis	10	15.4
Pancytopenia	5	7.7

cells were seen in more than two thirds of neuroblastoma, Ewing sarcoma and PNET. Fibroblastic reaction was observed in 14 (21.5%) most of them were neuroblastoma. Neurofibrillary matrix observed in 2 (3.1%) of the case, all were neuroblastoma, details are listed in Table 2. Immunohistochemistry staining was used to confirm the diagnosis in all the cases.

Bone marrow infiltration reflects on peripheral blood indices. Anemia was reported in 58 (89.2%), 84.5% of them were neuroblastoma, 6.9% were retinoblastoma and 3.7% of PNET and rhabdomyosarcoma (P=0.033). Leukopenia was seen in 18 (27.7%), 88.9% of them were had neuroblastoma, the rest had PNET. Thrombocytopenia was less reported as shown in Table 3, 11 (84.6%) were with neuroblastoma and 1 (7.7%) were with retinoblastoma and rhabdomyosarcoma. Bone marrow failure and pancytopenia was reported in 5 (7.7%) of the cases, 80% of them had neuroblastoma, the rest had rhabdomyosarcoma.

■ DISCUSSION

Hematological spread of pediatrics solid tumors and bone marrow involvement varies according to tumor type [15]. Bone marrow examination employed for primary diagnosis, tumor staging and prognostic significance [16]. We have found that almost a quarter of patients in our cohort has bone marrow involvement as a presenting feature along with other nonspecific features despite comprehensive clinical and radiological examination, 68.8% of whom end to be neuroblastoma. Furthermore, replacement of the bone marrow by metastatic solid tumor impairs normal hemopoiesis, resulting in myelopthesic anemia and various cytopenias consistent with other studies [17] which can be misdiagnosed as leukemia. To our knowledge this is the first Iraqi study which looked into bone marrow morphology and peripheral blood indices when bone marrow is involved by solid tumor in pediatrics.

The standard procedure for diagnosing bone marrow involvement, as recommended in several studies, included both bone marrow aspirate and biopsy. While tumor cells are frequently found in the bone marrow aspirate, the exact kind of tumor cannot always be determined in the absence of a bone marrow biopsy [18] which can be used subsequently for IHC study. The predominant microscopical morphology of metastatic tumors in bone marrow aspirate and biopsy, in this cohort, characterized by nonhemopoietic cell aggregates in small and large clusters with or without discrete cells. Less observed feature was neurofibrillary matrix which was observed exclusively in 3.8% of neuroblastoma cases while fibroblast reaction was associated with 25% of neuroblastoma and 20% of

retinoblastoma metastases. Widespread bone and bone marrow disorders can associate with bone pain, limping, and irritation [19]. 20% of the patients in our cohort complained of bone and joint pain and 9.2% had weakness in the lower limp, especially those with Ewing sarcoma, PENT and neuroblastoma.

Bone marrow replacement by metastatic cells may associate with symptoms of marrow failure in advance stages [15, 19]. The majority (89.2%) of these patients in this study had anemia. Moreover, twenty percent of the patients had thrombocytopenia while 7.7% of then complained of bleeding tendency. On the other hand, thrombocytosis was observed in 10 (15.4%) of our patients. In an earlier study, Penchansky and colleagues reported that thrombocytosis in children with solid tumors was more frequent in those who did not have bone marrow involvement (39% vs 10%) [18]. Later studies found a strong association between thrombocytosis and bone metastasis [20]. Platelet activation by cancer cells is found to be a critical process that results in platelets› prometastatic action [21]. Bone marrow failure and pancytopenia was observed in 7.7%.

In this study, and consistent with previous studies, neuroblastoma was the most frequent tumor with bone marrow metastasis [13]. Generally, neuroblastoma is the most prevalent extracranial solid tumor affecting children in Iraq [22]. In a unicenter retrospective study recoded the prevalence of solid tumors between 2006–2017, 38 out 135 were neuroblastoma [23]. The median age at diagnosis is approximately 18 months and rarely occur in children older than ten years [24]. This is in agreement with our findings in which all the patient were under the age of five. Apart of the constitutional symptoms which was reported by more than a third of our patients, abdominal mass was the most frequent clinical presentation reported by 57.7% consistent with other studies [24]. According to the literature, 70% of neuroblastoma patients had metastatic disease at diagnosis, with the most frequent metastatic locations being the bone, bone marrow, and liver [13]. Eighty percent of bone marrow involvement in our cohort were metastasized neuroblastoma, 11 (21.2%) of which were at diagnosis. The occurrence of bone metastases indicates a poor patient's outcome [13]. 80% of patient with bone marrow failure in this cohort had neuroblastoma.

Retinoblastoma is the second frequent solid tumor with bone marrow metastasis in our cohort (7%). A case series study reported 32 cases of retinoblastoma in Children Welfare Teaching during the period between 1999–2006, half of them had advanced stage [25] which is higher than what have reported in the literature (10–15%) [24]. Retinoblastoma is a cancer of the very young; two-thirds are diagnosed before 2 years [24]. In agreement with that, we found that the mean age of retinoblastoma patient with bone marrow involvement in our cohort was 6 months. In addition to ocular signs and abdominal mass which are the main presenting feature of the disease [24], anemia was reported by most of the patients. None of the patients suffered from bone marrow failure.

Skeletal and extra skeletal Ewing sarcoma constituted 9.2% of our cohort. Patients were older with an average of around six years, however, this was younger than what previous studies have observed, which is the second decade of life [26, 27]. In agreement with other series [24], we found that males were more affected by Ewing sarcoma. Back pain, extremity weakness, or altered sensation are common presenting features of primary or metastatic Ewing sarcoma [28]. In this study, beside skeletal involvement, abdominal or back masses were presenting features in PNET patients. According to several studies, metastatic diseases are present in 25–30% of patients at first presentation.

There were 2 (3.1%) rhabdomyosarcomas with bone marrow involvement in our cohort, both were females although epidemiological studies indicate a slight male predominance [29]. Rhabdomyosarcoma is the most frequent soft tissue sarcoma of infancy comprising roughly 4% of pediatric malignant neoplasms that can arise in almost any tissue in the body [29]. Orbital tumors, which account for 25% of head and neck cancers, often present as proptosis and occasionally ophthalmoplegia [29]. One of the patients in our cohort has orbital tumor while the other presented with an abdominal mass. Metastatic disease at initial diagnosis accounts for 15% to 20% of the patients with rhabdomyosarcoma [30]. The most common sites of distant metastasis are lung, bone marrow, bone, and distant lymph nodes [31]. Sever bone marrow failure complected one of the cases who was 2.5 years old. A recent study reveals that children with rhabdomyosarcoma and bone marrow metastases frequently have unusual original locations and numerous metastases, with initial presentation resembling hematological or other solid tumors [32].

As a single referral center study in a nation with low resources, the study was restricted by the number of referred patients and the immunohistochemistry panel that is currently available. A large proportion of the patients were referred form other governorates and continued their treatments back in their home cities, lack of computerized patients and death records hindered our ability to follow up them and record the outcome.

■ CONCLUSION

Bone marrow metastasis in pediatrics with nonspecific symptoms represent a diagnosis challenge that can be resolved by bone marrow biopsy. Neuroblastoma was the most often occurring solid tumor in Iraqi children that metastasized to the bone marrow. In a small fraction of these individuals, bone marrow failure may develop, although thrombocytosis may also occur.

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