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Original Research Article

Bone Marrow Invasion in Childhood Solid Tumors

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Abstract

Bone marrow invasion in pediatric solid tumors is an essential area of research, as it has a significant impact on prognosis and treatment strategies. Bone marrow metastases occur when non-hematopoietic malignant cells infiltrate the bone marrow, often leading to severe hematological disorders and high mortality rates if not identified early. The mechanisms of bone marrow invasion involve tumor cells escaping into the bone marrow, forming micrometastases which can then take on aggressive forms. Bilateral bone marrow aspirates and trephine biopsies (BMAT) are essential for accurate classification, as discrepancies in results can occur. In addition to their progressive nature, pediatric solid tumors are characterized by a high metastatic potential, particularly in the bone marrow. This retrospective study analyzes a series of 52 cases of solid tumors with bone marrow invasion, diagnosed in the hematology laboratory and pediatric hemato-oncology unit (UHOP) of the Hassan II University Hospital in Fez over a six-year period, from January 2016 to December2022. Evaluation of bone marrow involvement is a key factor in therapeutic orientation and assessment of response to treatment. The presence of bone marrow metastases is associated with a poor prognosis. The haematology-biology laboratory plays an essential role in detecting extra-haematopoietic cells suggestive of bone marrow metastases, over and above standard tests. Despite advances in our understanding of spinal cord metastases, challenges remain in early detection and effective treatment, necessitating ongoing research to improve outcomes for affected children. In this article, we review the epidemiology, molecular mechanisms, clinical diagnosis, treatment and prognosis of bone marrow invasion in solid tumors in the pediatric population.

Keywords: Bone marrow metastases, myelogram, trephine biopsy, bone marrow biopsy, solid tumors.

INTRODUCTION

Solid tumors in children metastasize to the bone marrow, and the search for bone marrow invasion plays an important role in extension assessment, classification, therapeutic evaluation and prognosis [1, 2].

Bone marrow metastases of solid tumors refer to a group of diseases that originate from non-hematopoietic malignant tumor cells invading the bone marrow through complex metastatic patterns. And can progress to diffuse bone marrow involvement if not diagnosed early, leading to severe hematological complications such as microangiopathic hemolytic anemia. Neuroblastoma is the most common etiology, followed by Ewing's sarcoma and rhabdomyosarcoma [2].

Although the study of solid tumors is receiving increasing attention, available data remains limited, mainly from isolated cases or small series, and the absence of consensus recommendations hinders optimal management. The prognosis remains unfavorable overall, due in particular to the late stage of diagnosis and the need to adapt treatment to the suppression of bone marrow function [1, 2].

Solid tumor metastases are rare and have a poor prognosis. Treatment options are carefully chosen because of the suppression of bone marrow function [2].

The aim of our work is to highlight the role of biology in the extension workup, and to identify the epidemiology, molecular mechanisms, clinical diagnosis, treatment and prognosis of bone marrow invasion in solid tumors in the pediatric population.

MATERIALS AND METHODS

A retrospective study of medullary invasion of solid tumors in children, analyzed in the hematology

laboratory and the pediatric hemato-oncology unit (UHOP) of the Hassan II University Hospital in Fez over a six-year period, from January 2016 to December 2022.

Epidemiological, clinical, biological and evolutionary data were collected from haematology laboratory registers and patient records (paper and electronic) hospitalized at the UHOP. The search for bone marrow metastases was based on myelograms performed at the hematology laboratory of the Hassan II University Hospital in Fez.

Inclusion criteria

All children under the age of 15 diagnosed with a solid tumor were included in the study.

Exclusion criteria

Bone marrow-invasive lymphomas, benign tumors and those without histological evidence were excluded from the study. Patients whose records could not be used were also excluded from the study.

Bone marrow was collected by aspiration from both iliac crests.

The myelogram was sent to the central hematology laboratory at CHU Hassan II, where the various slides were stained with May Grunwald Giemsa.

All slides were read by the biologist under a light microscope, using *10, *20, *40 and *100 objectives, looking for isolated extra-haematopoietic cells or arranged in syncytial clusters or grape clusters.

RESULTS

Epidemiological aspects

During the study period, 165 bone marrow samples were taken. Bone marrow invasion was reported in 31.51% of malignant solid tumors in children (fig. 1).

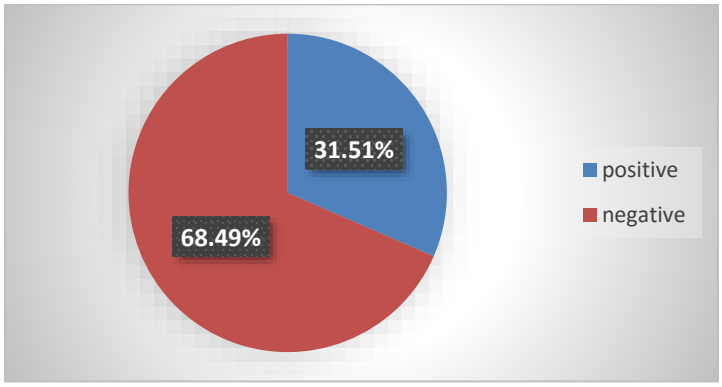

Figure 1: Prevalence of bone marrow invasion

In neuroblastoma, bone marrow invasion was reported in 67.30% of cases (35 cases), followed by retinoblastoma in 17.3% (09 cases), Ewing's sarcoma and nephroblastoma, each representing 5.76% (03 cases), and rhabdomyosarcoma in 3.84% (2 cases) (figure2).

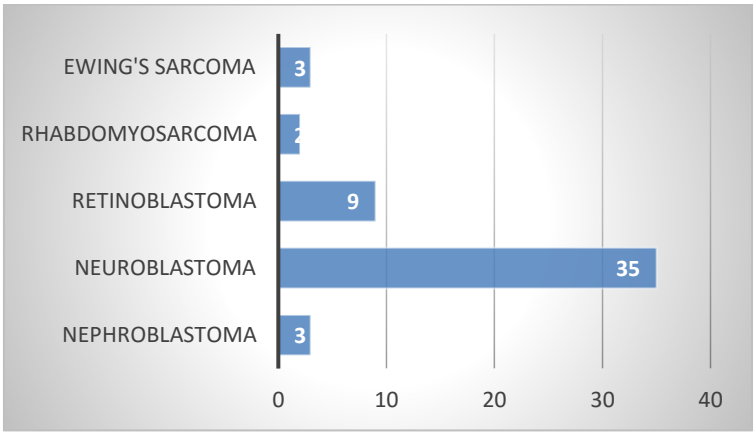

Figure 2: Distribution of bone marrow invasion according to tumor type

Socio-demographic characteristics

Among the 52 patients with bone marrow invasion, there was a slight male predominance at 51.92%, with a M/F sex ratio of 1.08.

The median age was 3.4 years, with extremes ranging from 4 months to 14 years. Of the 52 children, 45 had no pathological antecedents, while 7 patients had

a notion of parental consanguinity, 4 of which had first-degree consanguinity.

Diagnostic aspects Clinical

The time to diagnosis of solid tumors in our pediatric population varied considerably depending on the malignant primary tumor, ranging from 4 days to 3 years. The shortest delays were for neuroblastoma and nephroblastoma (between 4 days and two months), followed by retinoblastoma, with a diagnostic delay of between 20 days and four months, and then Ewing's sarcoma and rhabdomyosarcoma, with longer delays ranging from three months to 3 years. The clinical manifestations of discovery varied according to tumour type. Neuroblastomas were revealed by abdominal distension, abdominal pain, bone pain and altered general condition. Isolated swelling of the lower limb was the most prevalent mode of manifestation in Ewing's sarcoma and rhabdomyosarcoma. In retinoblastoma, leukocoria with decreased visual acuity and exophthalmos was the most frequent finding.

Among our patients, 62.4% presented another metastatic site other than bone marrow. Metastases were mainly lymph node (61.5%), bone (53%), liver and pleuropulmonary (17.4%). Other metastatic sites (7.3%) were the brain, orbit, skin and soft tissues. Extramedullary invasion was observed in neuroblastoma (64.5%), followed by rhabdomyosarcoma (14.7%), Ewing's sarcoma and retinoblastoma (both 10.4%). Bone scintigraphy was performed in 40.38% of our patients and showed secondary bone localization in 59.09% of cases.

BIOLOGICAL ASPECTS

All patients underwent a complete blood count (CBC), a standard biological workup, a tumor lysis workup, as well as specific analyses depending on the primary tumor. The results of the blood count showed anemia with a mean hemoglobin level of 10.3 g/dl, with extreme values ranging from 6.7 to 14 g/dl; mean white blood cell count was 6055/mm3, with values ranging from 810 to 14,160/mm3; mean platelet count was 355,000/mm3, with extreme values ranging from 11,000 to 502,000/mm3. All patients underwent bone marrow biopsy, which revealed infiltration in 70.5%. Medullary puncture for extra-haematopoietic cells was also systematically performed.

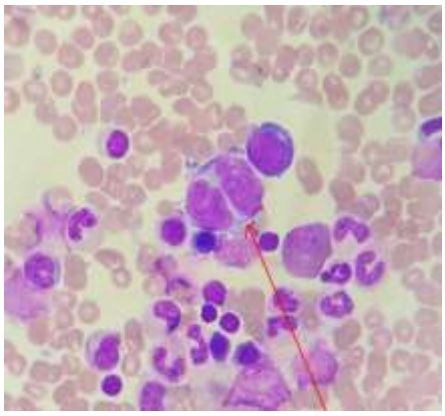

Figure 3: Image of bone marrow smear stained with MGG and read with M.O at the objective (x100), showing isolated extra-haematopoietic cells (retinoblastoma): Laboratory, Haematology Department, Hassan II University Hospital, Fez

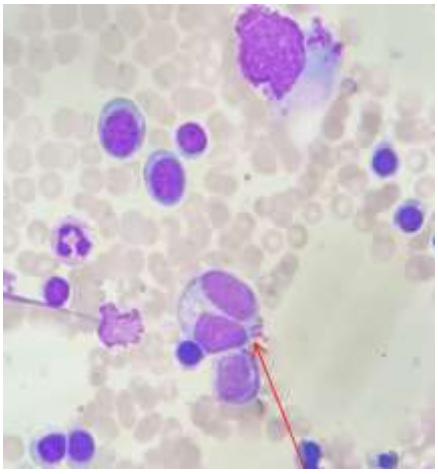

Figure 4: Image of bone marrow smear stained with MGG and read with M.O at the objective (x100), showing isolated extra-haematopoietic cells (rhabdomyosarcoma): Laboratory, Haematology Department, Hassan II University Hospital, Fez

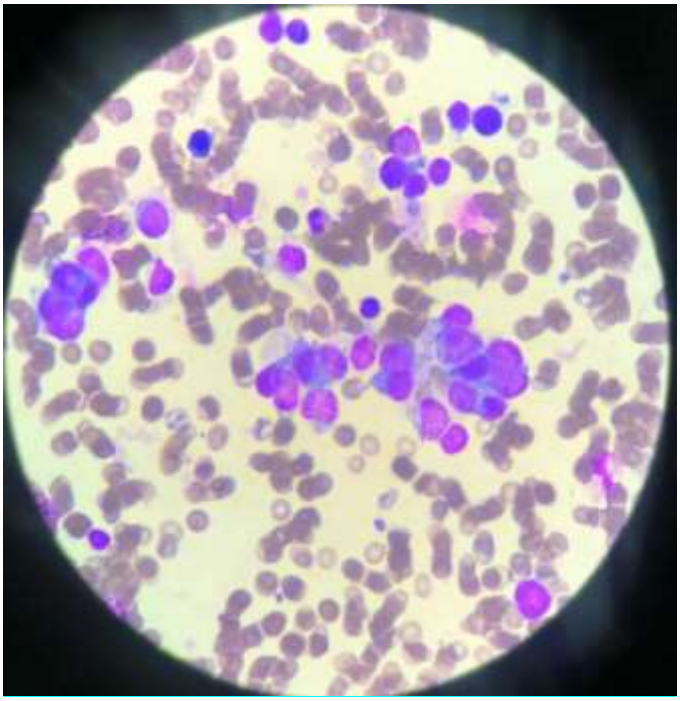

Figure 5: Image of bone marrow smear stained with MGG and read with M.O at the objective (x100), showing extra-hematopoietic cells grouped in syncitial clusters:) Laboratory, Haematology Department, Hassan II University Hospital, Fez

All patients with bone marrow metastases were put on chemotherapy, but 28% of children died during treatment.

DISCUSSION

Epidemiology:

Although they account for less than 2% of all cancers worldwide, solid tumors in children are considered relatively rare. Moreover, their low cumulative risk of development, estimated at between 1.0 and 2.5 per 1000 in children under 15, and their overall curable potential, may mitigate the perception of their seriousness. However, with incidence rising worldwide, cancer remains a major cause of mortality in children [3,4].

In the paediatric age group, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma and retinoblastoma are often cited as the most frequent solid tumours to invade the bone marrow [5,6]. Similarly, the most frequently detected bone marrow involvement was neuroblastoma.

Our study revealed a 31.51% prevalence of medullary invasion among pediatric solid malignancies, with neuroblastoma accounting for 67.30% of medullary invasions, followed by retinoblastoma (17.3%), Ewing's sarcoma and nephroblastoma (5.8%), and rhabdomyosarcoma (3.84%). This is similar to observations made in other international series [5,6]. Liang, *et al*. reported that neuroblastoma remains the solid tumor most frequently associated with bone marrow invasion, followed by Ewing's sarcoma and rhabdomyosarcomas [7]. This distribution is in line with our results.

DIAGNOSTIC METHODS

Bone marrow examination is essential for diagnosing a variety of disorders, including assessing the presence of metastases [8]. As well as playing a role in tumour staging, metastases can also help to search for the primary tumour [9]. The detection of metastases in bone marrow also influences the proposed treatment, as well as the clinical course, prognosis and survival of patients [7].

Positron Emission Tomography/Computed Tomography (PET/CT) has high sensitivity and specificity for the evaluation of bone marrow involvement in pediatric solid tumors [10]. Arslantas *et al*. concluded that PET/CT is highly effective in assessing bone marrow involvement in pediatric solid tumors. They recommend that PET/CT be the first step in diagnostic classification [10].

The diagnostic techniques used in our study concluded mainly bone marrow aspirates and trephine biopsies, confirming their central role in the detection of bone marrow metastases. Barbara Bain and Riley *et al*. have shown that these methods, although slightly invasive, remain the gold standard for identifying tumour cells in bone marrow [11, 12]. In parallel, the introduction of MRI and FDG-PET/CT has enabled better staging and more accurate identification of bone marrow metastases, particularly in patients with subtle lesions not visible on conventional biopsies [10]. In our

series,Magnetic Resonance Imaging (MRI) and Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) played a crucial role in confirming suspected diagnoses, bringing our practices into line with those recommended in the literature.

Additional diagnostic methods are needed in the context of bone marrow invasion, as shown by Schriegel *et al* in their study, who concluded that in neuroblastoma, flow cytometry and automated immunofluorescence achieved higher detection rates than traditional cytomorphology, demonstrating their importance in comprehensive diagnostic protocols [14].

Immunohistochemistry plays a crucial role in confirming the diagnosis of metastases and identifying the primary tumor site, particularly in cases of unknown primary cancers [13]. In our study, immunohistochemistry (IHC) was performed in most of our patients (45%), which is in line with the literature.

Although our study provides important insights into bone marrow invasion in pediatric solid tumors, it has certain limitations inherent in its retrospective nature. Indeed, the exclusion of lymphomas and benign tumors may have influenced the distribution of the cases analyzed. In addition, the lack of systematic molecular tests (such as flow cytometry) limits our ability to establish precise links between cellular phenotypes and clinical features [12]. In the future, it would be relevant to integrate these technologies to better understand the underlying molecular mechanisms and further personalize treatments.

Mechanisms of bone marrow invasion:

Invasion of the bone marrow by solid tumors involves several complex biological mechanisms, including cell migration and adhesion, alteration of the bone marrow microenvironment, angiogenesis and pro-survival factors[15].

The mechanisms underlying bone marrow invasion are not fully elucidated, but several hypotheses have been put forward. Tumor cells may use signaling pathways and adhesion molecules to enter and colonize the BM. The bone marrow microenvironment, rich in growth factors and cytokines, may also favor tumor cell survival and proliferation. Recent studies have highlighted the role of molecules such as CXCR4, a chemokine that facilitates tumor cell migration to the bone marrow [14]. A study by Schriegel *et al.* highlighted the key role of interactions between tumor cells and the bone marrow microenvironment, facilitated by molecules such as CXCR4 and VEGF [15]. These findings corroborate our clinical observations, where patients with neuroblastoma, known for its ability to highly express CXCR4, showed high rates of medullary invasion (67.30%). Similarly, VEGF-stimulated angiogenesis could explain the rapid progression of bone marrow metastases observed in certain aggressive forms of Ewing's sarcoma and rhabdomyosarcoma [15].

Therapeutic strategies:

Therapeutic strategies to combat marrow invasion of solid tumors in children involve a multi-faceted approach, focusing on novel therapies, immunotherapy and manipulation of the bone marrow microenvironment [16]. These strategies aim to improve outcomes for pediatric patients with malignancies such as neuroblastoma and Ewing's sarcoma, which are often resistant to conventional therapies [16].

The use of conditionally replicating adenoviruses has shown promise in purging tumor cells from bone marrow grafts, particularly in the case of neuroblastoma and Ewing's sarcoma, which are susceptible to adenoviral infection [16].

Autologous bone marrow transplantation (ABMT) is frequently used for pediatric solid tumors to mitigate the effects of high-dose chemotherapy, enabling more aggressive treatment regimens [17]. This method is particularly useful when compatible allografts are not available, as it provides a viable alternative for many children with malignant tumors [17]. In our study, treatment is essentially based on chemotherapy.

Prognosis:

Patient outcome showed a high mortality rate, with 15 deaths (28.84%) during the course of treatment, reflecting the severity of spinal cord involvement in these diseases. This figure is comparable to data reported in other studies, where spinal cord involvement is often associated with a poor prognosis [18].

Although these strategies are promising, challenges remain, particularly in the context of residual disease and the need to develop more effective treatments to improve outcomes for high-risk patients. Further research into the molecular mechanisms of bone marrow metastases is essential to develop more targeted and effective treatments [18].

CONCLUSION

The detection of bone marrow invasion in pediatric solid malignancies plays an essential role in the classification of certain tumors, prognostic assessment, extension workup and treatment planning, as well as in the evaluation of response to treatment.

A multidisciplinary approach could improve cure rates for patients with malignant solid tumors metastatic to the bone marrow, and prevent progression under chemotherapy. It would also be appropriate to establish a national registry of pediatric solid malignant tumors, in order to set up a well-defined circuit to reduce delays in care, both diagnostic and therapeutic.

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