Journal of Pre-Clinical and Clinical Research 2024, Vol 18, No 3, 246-249
www.jpccr.eu

CASE REPORT

Skin lesions as the first manifestation of metastatic neuroblastoma in an infant – case report

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Nowak E, Ostojska M, Osial N, Psiuk D, Nurzyńska-Flak J. Skin lesions as the first manifestation of metastatic neuroblastoma in infant – case report. J Pre-Clin Clin Res. 2024; 18(3): 246–249. doi: 10.26444/jpccr/191879

Abstract

Neuroblastoma is the most common extracranial solid tumour in the paediatric population. It is an embryonal tumour of the autonomic nervous system which arises in tissues of the sympathetic nervous system, typically in the adrenal medulla or paraspinal ganglia, and thus can present as mass lesions in the neck, chest, abdomen, or pelvis. The clinical presentation is highly variable. Mainly, the tumour is a mass that causes no symptoms; however, it can range from a primary tumour, a result of local invasion that causes critical illness, to a widely disseminated disease. The case is presented of a 6.5-month-old girl with hard, painless, purple-blue coloured subcutaneous nodules in the right and left subcostal area, which were the first manifestation of disseminated neuroblastoma 4S. The described case indicates that special oncological awareness should be maintained in every paediatric patient with undefined, non-characteristic skin lesions and subcutaneous nodules.

Key words

neuroblastoma, cutaneous metastases, neuroblastoma 4S, subcutaneous nodules

INTRODUCTION

Neuroblastoma is a malignant tumour of neural stem cells originating from the neural tube and neural crest, forming into the adrenal medulla and ganglia of the sympathetic nervous system. It is the most common childhood extracranial solid tumour which accounts for about 7–10% and 30–50% of childhood and newborns cancers, respectively [1, 2]. Most cases of neuroblastoma develop sporadically and occur with complex pathogenesis, chromosomal abnormalities and single-nucleotide polymorphisms. The familial neuroblastoma occurs in 1–2% of infants. The primary predisposition genes are *ALK* and *PHOX2B* [3]. Neuroblastoma can develop in any location where embryonic cells of the sympathetic nervous system occur. Most often it is located in the abdomen (60–80%), especially in the adrenal glands. Other locations include the posterior mediastinum, neck and pelvis [2].

The clinical presentation depends on the location of the tumour, the coexistence of metabolic disorders and the presence of metastases [4]. Most often, the symptoms of the disease are non-specific, for example, weakness, drowsiness, weight loss, unexplained fever and abdominal pain [5]. Patients may also experience symptoms associated with increased secretion of catecholamines, such as: paroxysmal sweats, facial flushing, headaches, palpitations or hypertension [2].

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Received: 29.05.2024; accepted: 01.08.2024; first published: 05.09.2024

The presence of metastases can actually be the first clinical indication of neuroblastoma. The most frequent location of metastases is the cortical bone and bone marrow, where metastases can cause bone pain, which leads to limping or refusal to walk, especially if it involves the lower extremity or pelvis. When the spine is affected, compression fractures can occur [6]. The oligosymptomatic course of the disease with predominance of uncharacteristic or general symptoms, results in delayed contact with a doctor. As a result, a significant percentage of children are diagnosed with neuroblastoma at stage 3 and 4 (according to the INRGSS classification – International Neuroblastoma Risk Group Staging System). Meanwhile, the course of the disease is closely related to the stage at diagnosis, the age of the child, and the histological and genetic features of the tumour. The prognosis ranges from spontaneous tumour regression to aggressive disease resistant to multimodal therapy [1, 2, 4].

CASE REPORT

A 6.5-month-old girl, developing properly so far, was referred to the Paediatric Surgery Clinic due to the presence of hard, painless, purple-blue coloured subcutaneous nodules in the right and left subcostal area, persisting for about 3–4 weeks. The abdominal ultrasound revealed a nodular lesion above the upper pole of the left kidney and hypoechoic lesions in the liver. Due to the suspicion of neoplasm, the patient was initially referred to the Department of Paediatric Surgery and Traumatology of the Children's University Hospital in

Lublin, Poland, to remove a subcutaneous nodule with a margin diameter of about 1 cm, located in the left subcostal region. The result of the histopathological examination of the collected material confirmed the presence of neuroblastoma of poorly differentiated subtype with poor stroma. Genetic examination revealed lack of N-Myc gene amplification. The performed studies and clinical data, indicated the presence of an adrenal tumour and metastatic foci in the liver, which supported the diagnosis of disseminated neoplastic hyperplasia of the neuroblastoma 4S N-Myc (-) type.

The patient was admitted to the Department of Paediatric Haematology, Oncology and Transplantology of the Children's University Hospital in Lublin in order to expand the diagnostics. She was in good general condition and did not seem to have any pain. She had no symptoms of infection, normal appetite, and urine and stool were excreted without any disturbance. Physical examination revealed a biopsy scar located in the left hypochondrium and an enlarged liver protruding about 3.5 cm below the right costal arch. The only abnormality detected by laboratory tests was an elevated level of neuron-specific enolase (NSE) – 26.15 ng/ml (normal range: 5.4 – 12.9 ng/ml).

Abdominal CT scan revealed an irregular focal lesion in the area of the left adrenal gland which was enhanced after administration of contrast material. Numerous calcifications within the lesion were also present. The results of chest CT scan and bone marrow biopsy did not show any abnormalities. Likewise, in scintigraphy (gamma scan) of the adrenal glands and other body regions, there were no pathological areas of 131I-MIBG accumulation.

After vascular access port implantation, chemotherapy was started according to the LINES scheme (Therapeutic Group No. 6, CAR/VP-16). In total, the patient received 4 cycles of chemotherapy. The overall tolerance of the treatment was quite good. Occasionally, such symptoms as malaise, poor appetite, retching and swelling of the upper lip occurred. In addition, after the first cycle of chemotherapy, the infant developed symptoms of upper respiratory tract infections, such as cough, runny nose, but with temperature within the normal range. Moreover, the administration of the fourth cycle of chemotherapy was postponed for 7 days due to the presence of neutropenia (230/μl, 3,9%).

After the end of chemotherapy, follow-up ultrasound showed regression of liver metastases. In abdominal MRI and CT scans with contrast, the residual lesion with numerous calcifications in the left adrenal gland was detected. These examinations also confirmed the regression of lesions in the liver.

DISCUSSION

In the described case, the first symptom which caught the attention of the parents and initiated extended diagnostics, were hard, painless, purple-blue coloured subcutaneous nodules in the subcostal area on the right and left sides of the body. Other symptoms that could suggest neoplastic disease, including general symptoms, were absent.

Skin lesions are a very common health problem in the paediatric population. They often cause concern to parents because they are visible to the naked eye. In highly developed countries, dermatoses and skin-related problems in children are the reason for up to 30% of primary medical care visits [7, 8]. Genneral practitioners should therefore be familiar with the most common skin lesions, as prompted paediatric dermatology consultation may not be possible. In Western countries, the most prevalent skin diseases are atopic dermatitis and allergic reactions, e.g. urticaria. In turn, in countries with a lower socio-economic status, infections – mainly bacterial and parasitic – rank higher [9].

The presence of subcutaneous nodules presents a big diagnostic challenge. There are 3 general categories of diseases associated with nodule formation: inflammatory or reactive, infectious, and neoplastic [10]. The clinical differential diagnosis of such changes in an infant is very broad and include, among others: cysts, haemangioma, abscess, cellulitis, sclerema neonatorum, subcutaneous fat necrosis of the newborn, dermal erythropoesis, cutaneous mastocytosis and neurofibromatosis [11, 12].

In addition, the neoplastic background of skin and subcutaneous lesions should not be forgotten. Subcutaneous nodules may be one of the symptoms of proliferative diseases, including both benign and malignant tumours, for example, all kind of leukemia (especially in congenital leukemia and acute myeloid leukemia), lymphomas, congenital Langerhans cell histiocytosis, metastatic neuroblastoma, metastatic rhabdomyosarcoma (especially alveolar type), metastatic rhabdoid tumour, primitive neuroectodermal tumour, choriocarcinoma, adrenocortical carcinoma, multiple xanthogranuloma, and infantile myofibromatosis [11, 12, 13, 14].

Metastatic nodules most often co-occur with leukemias. The term 'leukemia cutis' refers to infiltration of the dermis and subcutaneous tissues with leukemia cells. This may occur in any kind of leukemia, both congenital and childhood, including acute lymphoblastic leukemia, acute myelogenous leukemia, chronic lymphoblastic leukemia, and chronic myelogenous leukemia [15]. Statistically, it affects only about 3% of people diagnosed with the disease. Moreover, skin lesions are the very first sign of haaematological malignancy only in 7% of patients with leukemia cutis. It can present with various types of asymptomatic skin lesions, such as firm papules, nodules, plaques, diffuse eczema, erythema, purpura, petechiae, blisters, erosions and ulcers [16]. In general, the clinical appearance of skin lesions is not specific to a particular type of leukemia [15].

With regard to lymphomas, skin involvement is relatively rare in children. The most common form of cutaneous lymphoma is cutaneous T cell lymphoma [15]. This is a heterogeneous group of diseases characterized by monoclonal proliferations of T lymphocytes primarily involving skin, modified skin appendages, and some mucosal sites [17]. Although the clinical appearance of lesions is variable, most children present erythematous, scaly patches, papules or plaques located on the trunk and buttocks. There is also a variety of other paediatric lymphomas that have been associated with cutaneous manifestations, including subcutaneous panniculitis, such as T cell lymphoma, anaplastic large cell lymphoma, cutaneous B cell lymphoma, natural killer cell lymphoma, and Hodgkin lymphoma, among others [15].

In the case of Langerhans cell histiocytosis, up to 50% of patients may develop scalp, post-auricular, perineal and axillary involvement in the form of seborrheic dermatitis, multiple petechiae or yellowish-brown papules and nodules with central ulceration [18].

Typical skin lesions in metastatic rhabdomyosarcoma are asymptomatic solitary soft tissue masses. The cutaneous surface is frequently skin coloured, erythematous, or vascular in appearance. Lesions may have a history of rapid enlargement and are occasionally painful. The alveolar subtype has a tendency to metastasize and may cause multiple skin lesions [15].

Rhabdoid tumour may be present in the skin, especially in the head and neck area, as a solitary primary tumour or as one or more metastatic skin nodules. Metastatic disease is present in more than half of neonates at the time of diagnosis [14].

Primitive neuroectodermal tumour, choriocarcinoma, adrenocortical carcinoma are very rarely associated with skin changes and only single cases have been described [14].

Infantile myofibromatosis, the most common fibrous tumour of infancy, is characterized by the presence of myofibroblastic cells involving the skin, soft tissue, bones, and internal organs [19]. Characteristic nodular lesions are single or multiple, heterogeneous in size, grey-white in colour, and have necrosis or cystic change in the middle which can be visible to the naked eye [20].

Oncological concerns are aroused especially by undefined, non-characteristic cutaneous nodules in neonates and infants, which may be the first manifestation of a malignant disorder and thus require a prompt diagnosis. A patient with suspected cutaneous or subcutaneous lesions should undergo a whole body examination, firstly to determine the location, number, appearance and nature of the lesions. A complete blood count should then be performed to exclude bone marrow proliferative diseases. An ultrasound examination of the lesions is also a basic requirement. If neoplastic diseases with metastatic foci are suspected, abdominal ultrasound and chest X-ray are additionally indicated. In this case, radiological management can also be extended with a PET CT. A skin biopsy should always be part of the initial examination because the lesion's histology guides the recommendations for further investigations and the patient's clinical management [21].

In the presented case, the general practitioner referred the girl with multiple subcutaneous nodules to a surgeon. An excisional biopsy of the patient's subcutaneous nodule showed the presence of neuroblastoma cells which, combined with the ultrasonographically, detected an adrenal tumour, and metastatic lesions in the liver, which allowed for the diagnosis of 4S neuroblastoma.

Histologic examination of the cutaneous nodule in neuroblastoma 4S revealed a uniform, small cell, malignant tumour with or without Homer-Wright pseudorosette formation. The tumour cells showed neuron-specific enolase and synaptophysin reactivity, and neurosecretory (dense core granules) and neurotubules under electron microscopy [14].

Neuroblastoma is the most common cancer in the first year of life, but only 1% of cases start with skin metastases. They are most often located in the area of the head and neck, in the form of painless, mobile, hard subcutaneous nodules ranging in size from a few millimeters to centimeters, blue to purple in colour. They are similar to the changes observed in the 'blueberry muffin baby' syndrome, in which subcutaneous nodules are foci of extramedullary erythropoiesis. A case of co-existence of dermal erythropoiesis and metastatic neuroblastoma in a 'blueberry muffin baby' has been described [22]. In addition, neuroblastoma nodules show a characteristic blanching with surrounding erythema when stroked, which is associated with local release of catecholamines. Although subcutaneous nodules in the course of neuroblastoma are a manifestation of skin metastases, their presence indicates a form of neuroblastoma 4S with a good prognosis [11].

INRGSS classifies neuroblastoma according to its clinical, radiological and surgical characteristics into stages: 1, 2A, 2B, 3, 4 and 4S. Stage 4 – the dissemination of neuroblastoma to distant lymph nodes, bones, bone marrow, liver and/or other organs. Stage 4S (also called 'special' neuroblastoma) is defined as a localized primary tumour with dissemination to the liver, skin and/or slight dissemination to the bone marrow (under 10%) in children under one year of age [23]. One of the most important prognostic markers is the amplification of the MYCN oncogene. The multiplication of this gene located on the short arm of chromosome 2, is associated with rapid tumour progression and unfavourable treatment outcomes, regardless of the stage and the age of the child. It is found in ~30% of advanced neuroblastoma cases, and in about 8% of grade 4S neuroblastoma [2].

Based on histological, genetic and radiological testing, the patient in the presented case was diagnosed with neuroblastoma 4S without N-Myc amplification, according to the INRGSS classification. Considering the fact that the disease was disseminated with the presence of metastases in the liver, according to the European Low and Intermediate Risk Neuroblastoma protocol, the decision was made to include 4 cycles of carboplatin and etoposide chemotherapy.

CONCLUSION

Neuroblastoma is characterized by a disproportionately high mortality rate. On the other hand, there is a high rate of spontaneous regression, especially in newborns and infants. It is estimated that about 60 – 70% of children can be cured. The cure rate of infants diagnosed with neuroblastoma in stages 1 – 3 exceeds 90%. Although most patients with metastatic neuroblastoma of the skin have a favourable prognosis, some patients have an insidious course of the disease, with relapses and reduced quality of life. Establishing a diagnosis of metastatic neuroblastoma in an infant with cutaneous lesions, without a primary diagnosis, may be challenging as a broad list of diseases, both non-neoplastic and neoplastic, may have a similar clinical presentation. General practitioners, paediatricians and dermatologists, who are the first specialists to examine children with skin lesions, should include skin metastases in the differential diagnosis. In such cases, it is extremely important to diagnose early, at a low severity stage, and to implement appropriate treatment to inhibit progression of the disease. Therefore, in the case of undefined, suspicious skin lesions, as in the presented case, ultrasound examination should be performed first, followed by a skin biopsy as a part of the initial examination, because this can confirm the diagnosis. Moreover, the histology of the lesion guides the recommendations for further investigations and the clinical management of the patient.

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