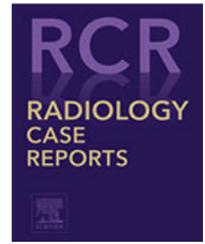


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Case Report

Integrated imaging of systemic Langerhans cell histiocytosis in an infant[☆]

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a myeloid neoplasm characterized by a clonal proliferation of CD1a+/CD207+ dendritic cells. Although individuals of any age can be affected, the disease is most common in infants younger than 5 years of age, especially males. A wide range of manifestations, from asymptomatic to aggressive, have been described, along with multiorgan involvement. Even though the majority of bone lesions are observed, skin, lymph nodes, brain and lungs can also be involved. The involvement of hematopoietic system, including bone marrow, liver and spleen, is less frequent yet associated with worse prognosis, due to a worse treatment response. Diagnosis of LCH is based on the integration of clinical, laboratory, and radiological data; however, only histopathological examination might confirm it. As far as the spleen involvement is concerned, according to literature, it has been reported in about 15% patients with multisystem involvement, nonetheless only a few cases show parenchymal lesions. The present study reports the case of an infant with LCH with multisystem involvement, including bone, skin, liver, and spleen, with evidence of parenchymal lesions.

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Introduction

Langerhans cell histiocytosis (LCH) is a rare hematological disorder previously known as “Histiocytosis X,” a nosological entity including Eosinophilic Granuloma, Letterer-Siwe disease and Hand-Schuller-Christian disease, a spectrum of conditions characterized by an abnormal oligonal proliferation of myeloid-derived dendritic cells with similar features to epidermal Langerhans cells of the monocyte-macrophage system [1,2].

The hallmark of LCH is the accumulation of histiocytic cells, which typically show positivity for CD1a/CD207 (Langerin) on immune-histochemical examination, in any tissue or organ. This infiltration is followed by chronic inflammation along with the formation of granulomas [3].

For a long time, LCH has been considered as a reactive proliferation of Langerhans cells due to an inflammatory stress, as suggested by the benign histological appearance of the CD207+ cell, the associated inflammatory infiltrate and the characteristic local and systemic cytokine storm. However, the recent discovery of oncogenic BRAF recurring mutations in LCH, along with rare KRAS and TP53 mutations, supports the classification of this disease as a neoplasm [4].

Among more than 100 histiocytic disorders showing various clinical manifestations and histological patterns, LCH is the most common histiocytic disease with an annual incidence of approximately 2-9 per million per years

Peak incidence is between 1 and 4 years of age, whereas a decreased incidence is observed thereafter [1,5–7]. Despite this, LCH may manifest at any age and has also been described in the elderly [8,9]. The disease occurs predominantly in males, with an M:F ratio of 3:2 [10,11]. Clinical presentation of LCH is widely variable, ranging from single indolent lesions to multisystem disease [4]. The most affected organs and systems are skin, bone, bone marrow, liver, spleen, lungs, lymph nodes and rarely the pancreas [12]. Bone is the most commonly involved site (80%), followed by skin (33%), whereas extraosseous involvement (pituitary, liver, spleen, bone marrow, CNS) is less frequently seen [1,12,13]. Possible complications are musculoskeletal disabilities, hearing problems, skin scarring, neuropsychiatric defects and secondary malignancies like leukemia [14]. Diagnosis is challenging and is performed by a combination of clinical features, radiological findings and histopathological evidence of accumulation of histiocytes in tissues, aggregating in CD1a and CD207 expressing granulomas [1,15]. Age of onset, multisystem involvement and rate of disease progression represent the main prognostic factors [16,17]. Therapy is not always necessary, since the disorder is self-limiting in most children except for patients with multisystem involvement, for whom a treatment based on steroids and chemotherapeutic agents is required [16]. Here, we present the case of an infant with multisystemic LCH involving bone, skin, liver and spleen.

Case report

A 33-day-old male infant presented to the Pediatric Emergency Room with diffuse skin lesions and hep-



Fig. 1 – Skin rash at hospital admission.

atosplenomegaly. The infant was born by normal spontaneous vaginal delivery following a full-term pregnancy. Birth weight was 3.7 kg. A skin rash involving the face was present at birth; however, it faded out within few days, as reported by his mother. In the following days, further skin lesions appeared over the whole body (Fig. 1).

For this reason, the infant was carried to the Pediatrician, who found the presence of the aforementioned skin lesions and hepatosplenomegaly. The infant was then taken to the ER, where all the necessary clinical-instrumental investigations were performed. On clinical examination, the infant presented with disseminated crusty skin lesions, similar to petechiae, which did not disappear on acupressure. Two other papular lesions were present on the scalp, the largest of which was about 2 cm. General conditions were fair, responsiveness and appetite were discrete. The urgently performed ultrasound of the abdomen confirmed the hepatosplenomegaly and showed the presence of multiple hypoechoic lesions in the hepatic and splenic parenchyma, the latter having the appearance of multiple images of point calcifications. Laboratory evaluation included complete blood count, serum electrolytes, liver enzymes, bilirubin, serum immunoglobulins and inflammatory makers, all of which were within normal limits, except for mild anemia and elevated CRP at 16.53 mg/dL (normal range: 0.5-1.0 mg/dL).

Considering the clinical-laboratory and instrumental findings, the infant was admitted to the Pediatric Ward for further investigations.

At admission, serological tests were performed to search for main perinatal (TORCH, VDRL, TPHA, EBV) and respiratory infections, with negative results, except for HSV IgG positivity.

A radiographic skeletal survey, a trans-fontanelar ultrasound and several clinical evaluations, including dermatological, neurological, cardiological, and hematological consultations, were also performed.

The skeletal radiograph showed 2 gross intraosseous osteolytic areas in the proximal epiphysis-metaphysis of the fibula, with interruption of the cortical bone, and in the proximal-middle diaphyseal part of the tibia (Fig. 2); a further

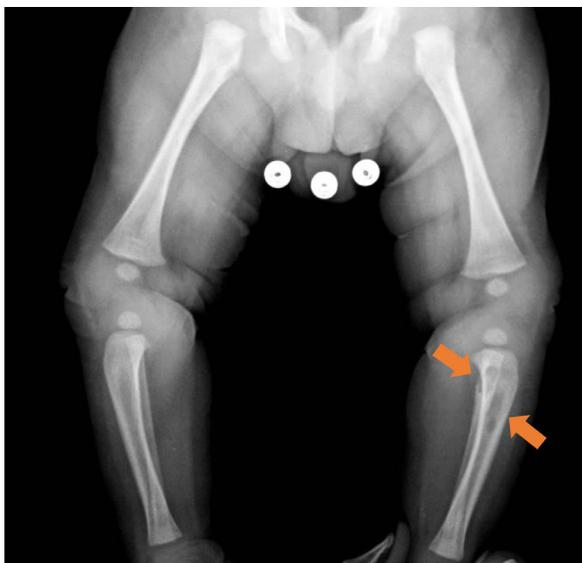


Fig. 2 – Bone radiograph shows 2 gross intraosseous osteolytic areas in the proximal epiphysis-metaphysis of the fibula, with interruption of the cortical bone, and in the proximal-middle diaphyseal part of the tibia (arrows).



Fig. 3 – Bone radiograph shows area of radiolucency in the context of the proximal metaphysis of the right femur (arrow). There is also visibility of the 2 osteolytic areas of fibula and tibia.

area of radiolucency was observed in the context of the proximal metaphysis of the right femur (Fig. 3).

Trans-fontanelar ultrasound did not show abnormalities in the brain parenchyma.

A skin biopsy of 2 lesions from the abdominal region and the left thigh respectively revealed diffuse proliferation of histioid cells (S100 +, CD1a +, Langerin +), and skin infiltration with histiocytes (CD68+). Genetic analysis also showed mutation of the BRAF gene.

This constellation of findings led to the diagnosis of multisystem Langerhans cell histiocytosis (LCH), therefore the infant was referred to our Department of Paediatric Haematology and Oncology.

The US examination of the abdomen performed at our Department substantially confirmed the findings of the previous ultrasound executed in the ER, ie, hepatosplenomegaly and multiple hypoechoic lesions of various sizes in both liver and spleen, the majority of which were featured by tiny internal echoes (Fig. 4).

On total body CT performed with contrast agent, liver and spleen appeared enlarged with an inhomogeneous parenchymal structure due to the presence of multiple hypodense nodular formations with hyperdense peripheral labrum (Fig. 5). Moreover, multiple osteolytic lesions of the pelvis were visible, on the iliac wings bilaterally, on the pubis and the left ischium in particular (Fig. 6). Additional bone injuries affected lumbar vertebral metamers, with micro lacunar aspect (Fig. 7), the proximal third of the clavicle and the body of the right scapula as well, with interruption of the bony cortex (Fig. 8).

The infant was therefore enrolled in the LCH-IV protocol, group 1 (patients with MS LCH), in order to receive a standard prednisone/vinblastine regimen.

Discussion

Langerhans cell histiocytosis is an uncommon disease featured by Langerhans cells' clonal proliferation and accumulation in various organs. The clinical presentation and the outcome of LCH depend on the patients' age, the number of lesions and the degree of organ dysfunction at initial diagnosis.

The current classification system identifies 2 types of LCH referring to the number of involved sites [18,19]: single-system LCH (unifocal or multifocal) involving a single organ or system such as bone, skin, lymph nodes, lung and central nervous system, thymus or thyroid less frequently; multisystem LCH involving 2 or more organs or systems, instead [7,20].

Approximately 65%-70% of patients are affected by the single system disease [21,22], whereas the multisystem form is observed in 10% of LCH cases and has a poor prognosis, being often fatal. It is typically diagnosed in the first 2 years of life [23].

Furthermore, MS-LCH can be divided into a low-risk group and a high-risk group, evaluating risk organ involvement, ie, bone marrow, liver, and spleen [24,25]; lung is no longer considered as a risk organ [26,27]. The involvement of these sites leads to a worse treatment response and is consequently associated with worse prognosis.

LCH frequently emerge with a skin rash, as observed in our patient, often followed by other nonspecific symptoms such as fever, lack of appetite, weight loss, fatigue, irritability [28,29]. Signs of multiple organ failure have also been found, especially in the youngest children with MS disease [21], including, in order of decreasing frequency, skeleton (80%), skin (33%), pituitary (20%), liver, (15%), spleen (15%), bone marrow (15%), lung (12%), and central nervous system (CNS) without pituitary involvement (5%) [1,12].

Bone involvement is mostly unifocal and commonly appears as a painful tumor formation in a localized area [30]. Any bone may be involved, excluding hands and feet [7,24,31].

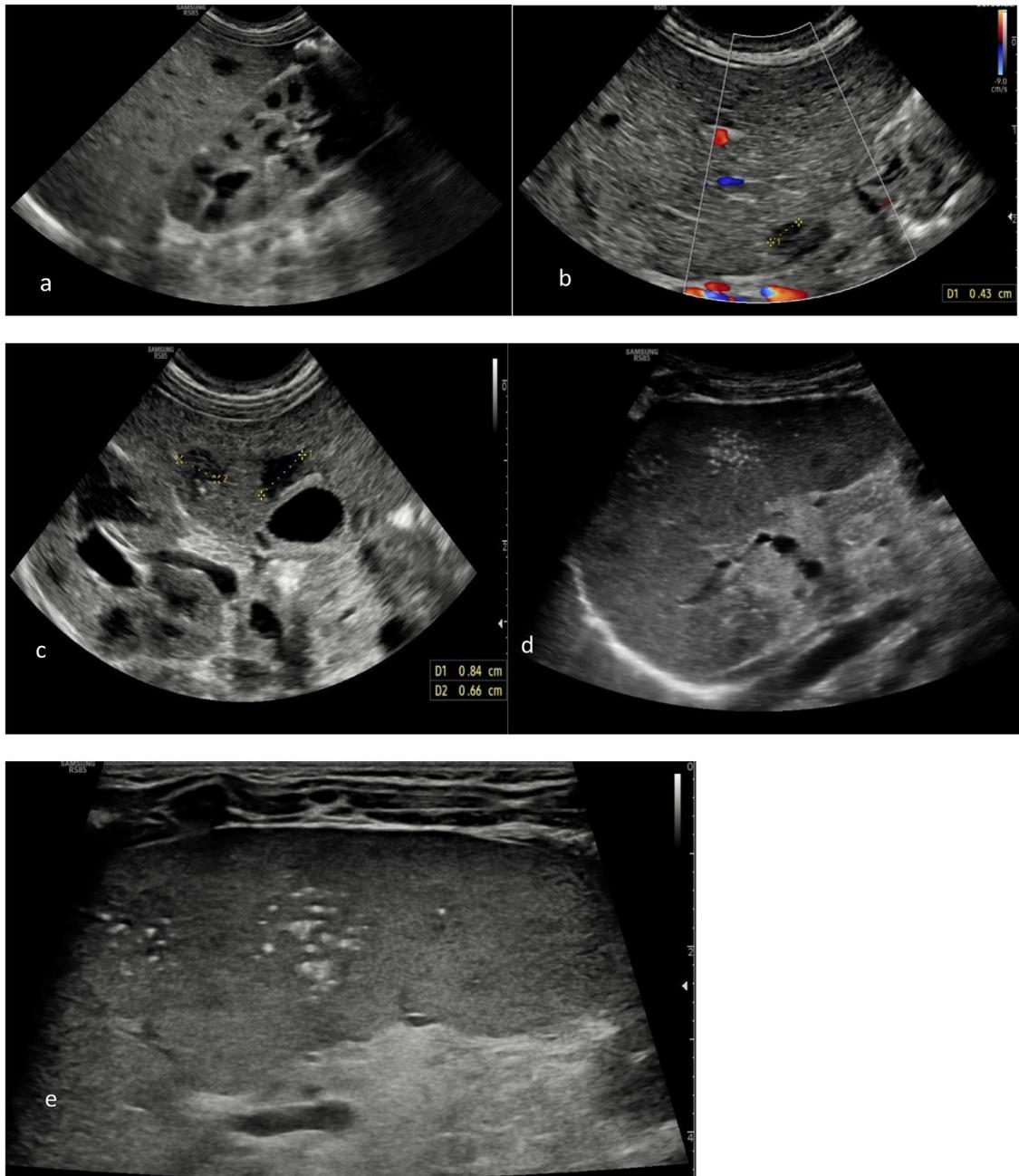


Fig. 4 – (a-e). Ultrasound imaging of the abdomen shows hepatomegaly with multiple hypoechoic parenchymal lesions (a-c) and splenomegaly with hypoechoic lesions and intralesional hyperechoic foci (d, e).

However, flat bones seem to be favored, those of the skull in particular (orbit and mastoid), followed by mandible, ribs, pelvis, spine (including vertebral bodies, with frequent presence of a vertebra plana) [1,30,23,32], as well as the long bones, especially femur, as observed in our infant. At imaging, radiograph typically shows single or multiple osteolytic lesions, without marginal sclerosis or periosteal reaction [33].

Cutaneous involvement normally presents as erythematous papules or pustules, which can mimic a seborrheic dermatitis or eczema [7]. In children affected by neonatal form, as the case we report, disseminated brown to red papules with common central ulceration can be observed [1].

The hematopoietic system, including liver, spleen and bone marrow is commonly involved in very young children and represents a poor prognostic sign.

Hepatic involvement has been described in only 15% of LCH patients, although it is relatively frequent in the multi-system LCH (representing up to 60% of the cases) [3,34]. It often presents with hepatomegaly (liver > 3 cm below the costal margin in the midclavicular line), which may be accompanied by signs of organ dysfunction, as increased transaminases, hypoalbuminemia, jaundice and/or clotting factors deficiency [20,35]. Imaging findings can be various, due to the histopathological evolution of the process, consisting in 4 progressive

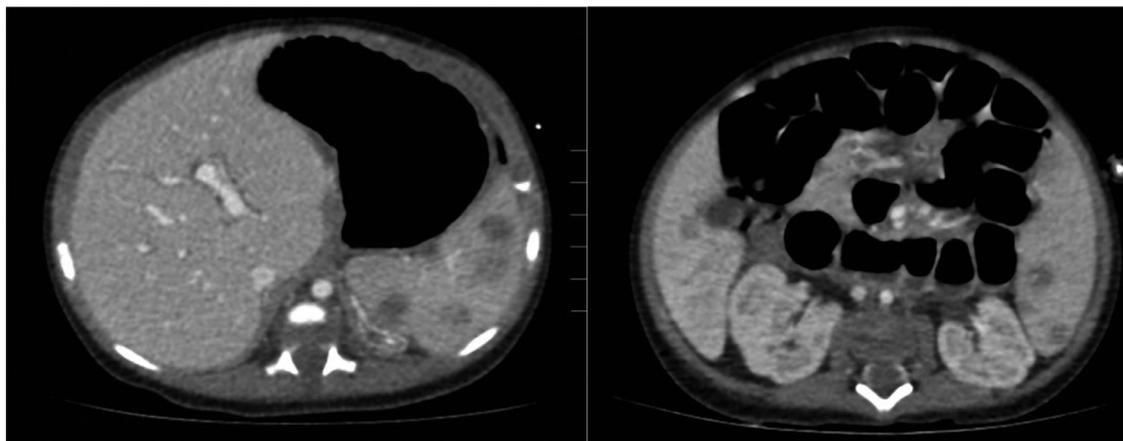


Fig. 5 – CT scans with contrast agent of the abdomen show multiple hypodense nodular formations with hyperdense peripheral labrum into liver and spleen.

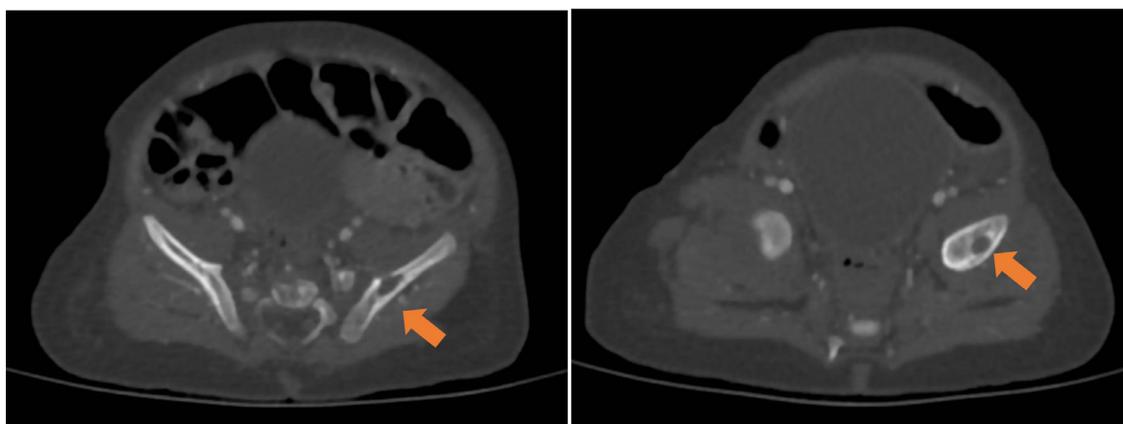


Fig. 6 – CT scans (bone window) of the pelvis show multiple osteolytic lesions (arrows).

phases from an initial proliferative phase to a final fibrous phase [36]. In the early stages, hepatomegaly and parenchymal lesions are the most common findings, which are likely to be hypoechoic at US and hypoattenuating at CT; the fibrous phase, instead, typically shows a dysmorphic and nodular appearance of the liver parenchyma due to periportal fibrosis. Sclerosing cholangitis, which is progressive and may eventually require liver transplantation, is a possible evolution of the late stage due to biliary sclerosis [3,6,37].

Splenic involvement is not frequent, affecting about 15% of patients with LCH and it is mostly found in subjects with systemic disease. It may be either the consequence of parenchymal infiltration by Langerhans' cells or might be secondary to portal hypertension as a result of periportal fibrosis. The most characteristic radiological finding of splenic affection is represented by splenomegaly (enlargement > 2 cm below the costal margin in the midclavicular line), typically followed by hypersplenism and subsequent cytopenia. In our patient, however, we could observe, along with splenomegaly, the presence of parenchymal lesions both on abdominal ultrasound and on CT scan. The literature only describes a few cases of splenic involvement with parenchymal lesions [38,37]. At CT, they be-

come evident as hypodense nodules with ring enhancement, similar to those observed in liver. At US imaging, they appear as hypoechoic nodules [37]; nevertheless, a hypoechoic ultrasound appearance with multiple internal hyperechogenic foci, seen in our case, has not been described yet.

Treatment, at present, is only recommended for patients with extensive disease or symptomatic lesions. Asymptomatic patients and those with single-system disease usually require observation, as they are known to heal spontaneously. In case of unifocal lesions, curettage or surgical excision might be performed. Despite advances in understanding the pathogenetic mechanisms of LCH, treatment for disease with multi-system involvement is controversial. The current standard of frontline care for multifocal LCH remains systemic multiagent chemotherapy. The most common chemotherapeutic agents are vinblastine, prednisone, etoposide and methotrexate, with a vinblastine/prednisone association regimen employed as first line therapy in this setting, to date [39]. In the present study, the patient was found to have a multiorgan form of the disease, thus he underwent a systemic treatment with prednisone/vinblastine. In case of severe and refractory LCH, patients may benefit from other therapies, including monoclonal

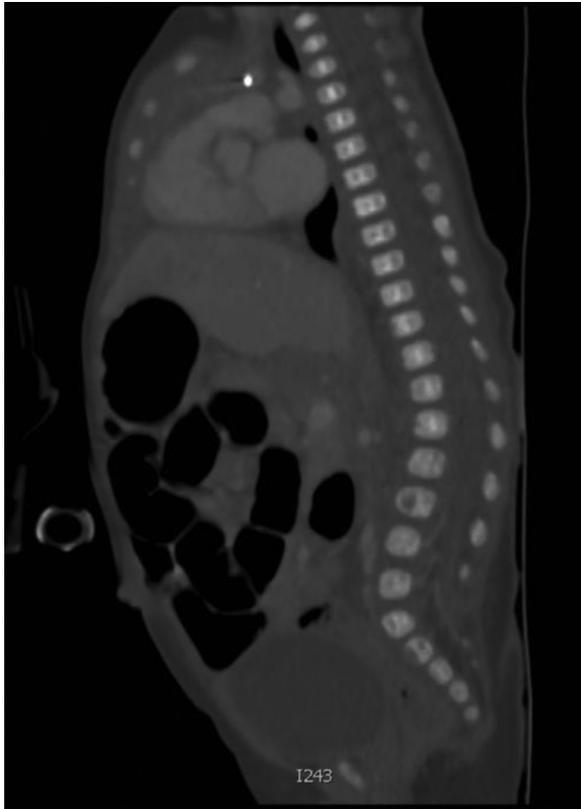


Fig. 7 – Sagittal TC reconstruction (bone window) shows some osteolytic lesions of the lumbar metamers.

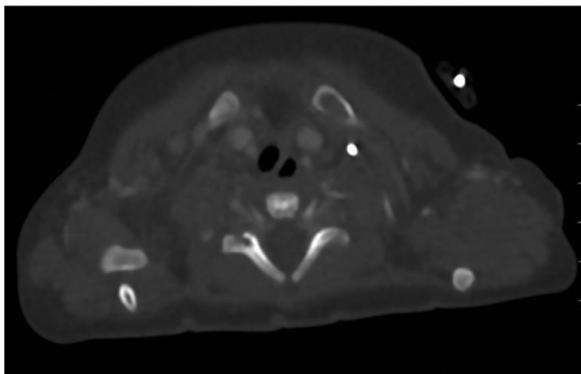


Fig. 8 – Axial CT scans of the upper thorax (bone window) show multiple osteolytic lesions affecting the proximal third of the clavicle and the body of the right scapula.

antibodies against CD1a, CD207 or CD52, BRAF V600E inhibition and bone marrow transplantation [4,40–42].

Patient consent

Informed written consent was obtained from the parents of the infant for the publication of the case report and of all the related images.

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