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CASE REPORT

Unusual cause of skin nodules in a child – case report

Michalina Horochowska[1], Jacek Jagiełło[2], Jadwiga Węcławek-Tompol[1], Marta Rzeszutko[3], Anna Zimny[2], Marek Ussowicz[1], Bernarda Kazanowska[1]

[1]Department of Paediatric Bone Marrow Transplantation, Oncology, and Haematology, Wroclaw Medical University, Wroclaw, Poland
[2]Department of General and Interventional Radiology and Neuroradiology, Wroclaw Medical University, Wroclaw, Poland
[3]Department of Pathomorphology, Wroclaw Medical University, Wroclaw, Poland

ABSTRACT

We report a four-year-old boy with a skin lesion that was misdiagnosed as an abscess and unsuccessfully treated with systemic antibiotics and drainage. Due to its progression, the child underwent a biopsy, which revealed myeloid sarcoma. The histopathological verification at the referral centre changed the diagnosis to an anaplastic large-cell lymphoma (ALCL) with internal organ involvement. This subtype of paediatric lymphoma usually manifests as a systemic disease, and isolated skin infiltration is rare. The patient was treated according to the ALCL-99 protocol and achieved remission. Five months later a systemic lymph-node relapse was diagnosed. Salvage chemotherapy was administered and allogeneic stem cell transplantation was performed, which resulted in sustained remission. Skin infiltrates are commonly seen in children, and routine diagnostics is usually sufficient for a proper medical care. The diagnostic difficulties in the reported patient emphasise the need for observation and invasive diagnostics in non-responding cases.

KEY WORDS:

T-cell lymphoma, anaplastic large-cell lymphoma, anaplastic lymphoma kinase, CD30+.

INTRODUCTION

The entities commonly manifesting by skin nodules in children are numerous, and the differential diagnostics must include infectious, inflammatory, and malignant causes and congenital defects. Early evaluation of skin nodules should include its size, duration, location, colour, consistency, growth speed, and possible itchiness or soreness [1, 2]. Approximately 1–2% of skin nodules excised in paediatric patients examined by histopathological examination prove to be malignant. Warning signs of malignancy are high-speed growth, unmovable and solid consistency, diameter over 3 cm, ulceration, and their presence in the neonatal period [3]. The clinical problem with skin nodules in children is not very common, but atypical manifestation or progression on antibiotic therapy warrants an active approach [4]. According to Infectious Diseases Society of America (IDSA) recommendations, antibiotic therapy of skin and soft tissue infections should be effective within seven days, and therapy failure at the seven-day mark should lead to invasive diagnostics. In addition, the infiltration of the skin without apparent infectious cause should prompt the invasive diagnostics with biopsy for unusual pathogens and malignancies [5]. We report a boy with a skin nodule, who was diagnosed by a primary care physician, and due to unusual clinical course was eventually treated at the specialistic centre.

ADDRESS FOR CORRESPONDENCE:

Michalina Horochowska, Department of Paediatric Bone Marrow Transplantation, Oncology, and Haematology, Wroclaw Medical University, 213 Borowska St., 50-556 Wroclaw, Poland, ORCID: 0000-0002-8564-917X, e-mail: m.horochowska@gmail.com

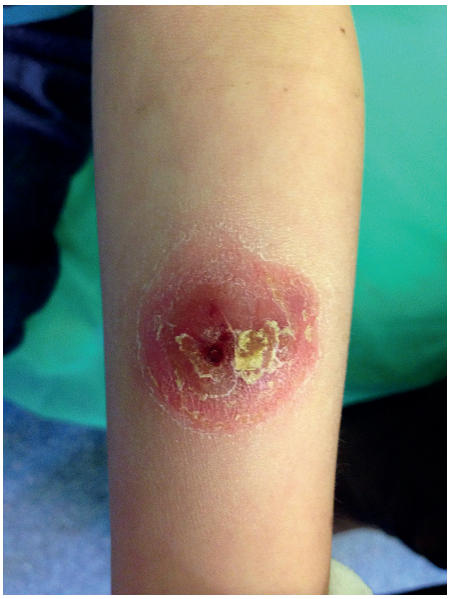

FIGURE 1. Picture of the left forearm. The nodular change with a diameter of 6 cm with an ulceration in the centre

CASE REPORT

In 2015 the mother of a four-year-old boy noticed a red spot with 1 cm diameter on her son's left arm. Initially the family doctor started topical therapy, with no effect. After three weeks, the lesion enlarged to 3 cm in diameter, with dark red, stiff, and smooth surface. The skin lesion was surgically incised twice, and bloody fluid was aspirated. During the second procedure the drainage was placed, and a yellow discharge was evacuated. The patient started antibiotic therapy with cefuroxime and amoxicillin with clavulanic acid. Due to clinical progression, the patient continued therapy at the Department of Paediatric Infectious Diseases, where an enlarged axillary lymph node was found and the patient was treated with amikacin and clarithromycin. One month later the lesion size increased and skin ulceration appeared, as well as an enlarged axillary lymph node with the diameter of 2–3 cm. Due to suspected atypical mycobacteria infection, microbiological cultures were performed, but they revealed no pathogens. The subsequent surgical debridement, and cytological and histopathological examinations eventually revealed the diagnosis of infiltrate identified as myeloid sarcoma. With this diagnosis the patient was transferred to the Department of Paediatric Bone Marrow Transplantation, Oncology, and Haematology.

On admission the boy was in a good condition, without major complaints. The physical examination revealed a 6 cm nodular skin lesion with a central ulceration, located on the left forearm (Fig. 1). The laboratory tests showed lowered haematocrit of 35.9 %, lowered MCV of 71.8 fl, increased platelet count of 508,000/µl, increased activity of alkaline phosphatase 529 U/l, and LDH 253 U/l. After fever recurrence, the patient started antibiotic therapy. Due to observed progression and suspected

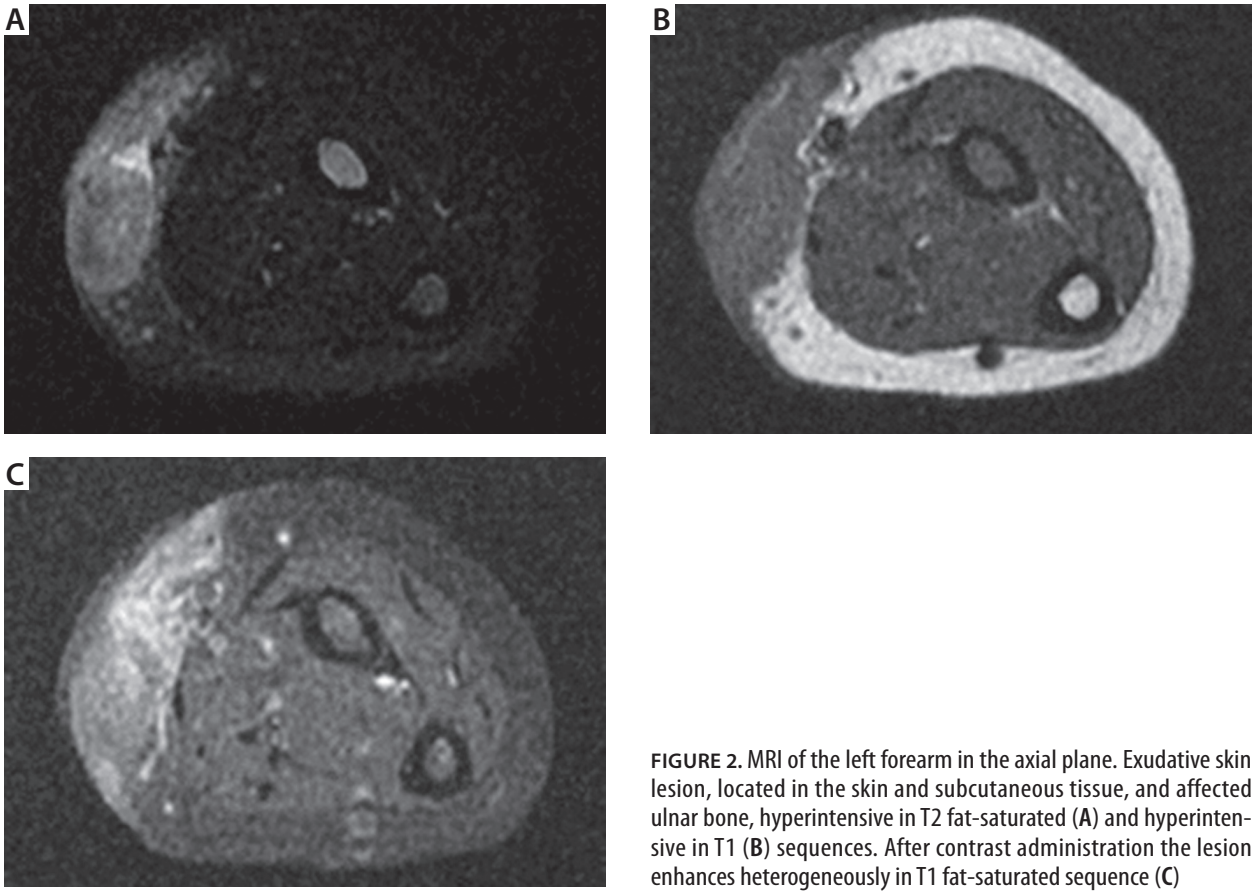

FIGURE 2. MRI of the left forearm in the axial plane. Exudative skin lesion, located in the skin and subcutaneous tissue, and affected ulnar bone, hyperintensive in T2 fat-saturated (**A**) and hyperintensive in T1 (**B**) sequences. After contrast administration the lesion enhances heterogeneously in T1 fat-saturated sequence (**C**)

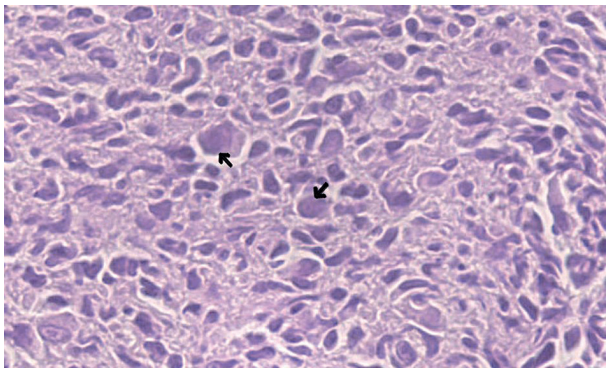

FIGURE 3. Micrograph of an anaplastic large cell lymphoma. The tissue sample was collected by surgical excision. The arrow indicates typical hallmark cells with lobulated, eccentric, and prominent nuclei typical for ALK-positive ALCL. Stained using haematoxylin and eosin (H+E)

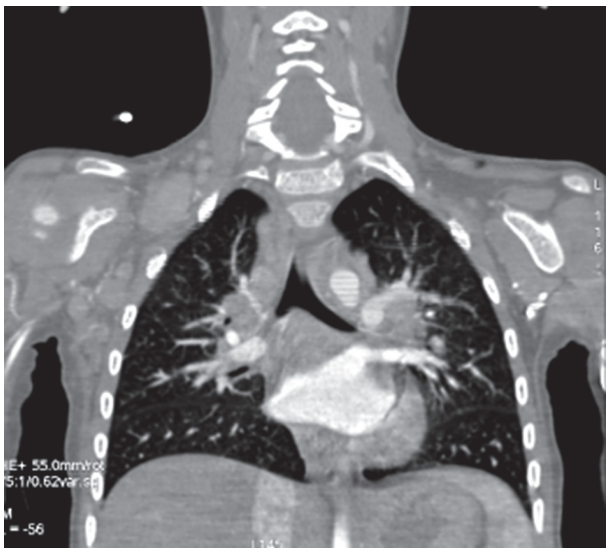

FIGURE 4. CT of the chest in the coronal plane. Multiple enlarged lymph nodes in the mediastinum, both axillae, clavicular regions, and neck

malignancy, the boy underwent a bone marrow biopsy, which revealed no abnormalities. An imaging study – magnetic resonance imaging of the left forearm – showed skin infiltration (Fig. 2).

The re-evaluation of the initial diagnostic material sample revealed anaplastic lymphoma kinase-positive anaplastic large cell lymphoma (ALK+ ALCL) (Fig. 3). The examination of cerebrospinal fluid and bone marrow smear showed no involvement. ALCL was classified as stage III, and the patient started chemotherapy according to the ALCL-99 protocol, resulting in complete remission (Table 1).

During routine check-up five months after the end of the treatment, ultrasonography revealed multiple enlarged pathological axillary and one supraclavicular lymph node/s on the right-hand side. The lymph node biopsy confirmed ALCL relapse, and on re-staging enlarged lymph nodes in the mediastinum, hila of both

TABLE 1. First-line treatment

Pre-phase course (course P)					
Days	1	2	3	4	5
Dexamethasone	•	•	••	••	••
Cyclophosphamide	•	•			
Intrathecal injection of methotrexate, cytarabine and prednisone	•				
Course A					
Days	1	2	3	4	5
Dexamethasone	••	••	••	••	••
Methotrexate	•				
Intrathecal injection of methotrexate, cytarabine and prednisone	•				
Ifosfamide	•	•	•	•	•
Cytarabine				••	••
Etoposide				•	•
Course B					
Days	1	2	3	4	5
Dexamethasone	••	••	••	••	••
Methotrexate	•				
Intrathecal injection of methotrexate, cytarabine and prednisone	•				
Cyclophosphamide	•	•	•	•	•
Doxorubicin				•	•

• one dose

lungs, right armpit, right and left supraclavicular fossa, and in the submandibular region were found (Fig. 4).

Second-line treatment was introduced, and the boy received two blocks of chemotherapy: ICM block (ifosfamide, carboplatin, mitoxantrone) followed by ICI (ifosfamide, carboplatin, idarubicin) (Table 2), according to the protocol for relapsed ALCL. Subsequently the patient was given weekly doses of vinblastine. No complications were observed during the treatment. Following donor selection, the boy underwent allogeneic haematopoietic stem cell transplantation (HSCT) from a matched, unrelated donor after conditioning with total body irradiation and megachemotherapy containing thiotepa, etoposide, and anti-thymocyte globulin. During the peri-transplant period second-grade mucositis and fever of unknown origin occurred. The mucositis required the application of total parenteral nutrition and morphine. To date, three years after HSCT, the boy remains in complete remission and shows full donor chimerism.

DISCUSSION

ALCL is a rare malignancy in children, which was originally discovered and described by Stein *et al.* in 1985, who reported a tumour with expression of Ki-1 antigen, later classified as CD30+ [6]. ALCL belongs to the ag-

TABLE 2. Second-line treatment

Course ICM						
Days	1	2	3	4	5	6
Intrathecal infusion of methotrexate, cytarabine, and prednisone	•					
Mitoxantrone	•	•				
Carboplatin		---	---	---	---	
Ifosfamide		---	---	---	---	---
Course ICI						
Days	1	2	3	4	5	6
Intrathecal infusion of methotrexate, cytarabine and prednisone	•					
Idarubicin	•	•				
Carboplatin		---	---	---	---	
Ifosfamide		---	---	---	---	---

• – one dose, --- – continuous infusion

gressive non-Hodgkin lymphomas arising from T cells or null lymphocytes and is classified by the World Health Organisation into two subtypes: anaplastic lymphoma kinase (ALK)-positive and ALK-negative ALCL [7]. ALCL accounts for 2% to 3% of all non-Hodgkin lymphomas in the entire population and 10–15% among children and young adults. It is characterised by large lymphoid cells presenting with anaplastic, pleomorphic, or immunoblastic morphology [8]. Nowadays the diagnosis is based on morphological criteria and on the expression in the tumour cells of the CD30+, EMAs (epithelial membrane antigen), and ALK antigens [9]. CD30 is a 120 kD transmembrane cytokine receptor of the tumour necrosis factor (TNFR) receptor family, which plays pleiotropic biological functions via stimulating different signalling pathways in different cell types and is able to promote the cell proliferation or induce apoptosis. The diagnosis of ALCL was originally based on the consistent expression of CD30+, but it can also be detected in activated B- and T-lymphocytes, Reed-Sternberg cells, other types of malignant lymphomas and rare solid tumours such as germ-cell tumours. In the ALCL cells its activity is modified by the expression of NPM-ALK protein, which binds to TNFR proteins and stops CD30-mediated cell proliferation [10]. It has been reported that in ALCL the overexpression and activation of CD30 reduces cell proliferation and induces cycle arrest [11, 12].

NPM-ALK protein is a product of a fusion gene formed by the translocation of t(2;5)(p23;q35), which can be found in 80% of cases of ALCL. The t(2;5) translocation leads to a fusion of ALK and nucleophosmin (NPM). ALK is a transmembrane receptor that expresses exclusively in the cells of the nervous system, belongs to the insulin receptor superfamily, and plays a significant role in the development of the brain [11]. NPM is a nuclear protein involved in ribosome biogenesis [13]. The NPM-ALK fusion encodes an 80 kD protein, which can localise in cytoplasm as well as in the nucleus of tumour cells [14]. NPM-ALK presence leads to overexpression and constitutional activation of ALK protein domains, resulting in ALK-mediated oncogenesis through uncontrolled proliferation of malignant cells [9].

Based on genetic and histopathological findings, immunophenotype, and clinical picture, ALCL can be divided into four subtypes: primary systemic ALCL (S-ALCL) with or without ALK expression (ALK+ or ALK–), primary cutaneous ALCL (C-ALCL), and breast implant-associated ALCL [7]. The clinical presentation of the disease is different according to the type of ALCL. Systemic lymphomas infiltrate lymph nodes in distant parts of the body and can form extranodal tumours. ALK+ ALCL occurs mainly among children and young adults, especially males, and correlates with advanced systemic disease, generalised lymphadenopathy, and extranodal involvement. It has been reported that ALK+ ALCL compared to ALK– has significantly better prognosis, due to chemosensitivity [9, 11]. C-ALCL presents as a reddish skin lesion with ulceration in different parts of the body, which may extend to regional lymph nodes [15]. C-ALCL occurs mainly in adults and shows no sex predominance. S-ALCL appears predominantly in children, more commonly in males. Nodal disease presents with frequent involvement of extranodal sites, with cutaneous involvement in 20% of cases. Simultaneously, in all kinds of ALCL, systemic symptoms may occur [16].

Children with C-ALCL are rarely diagnosed and are considered a low-risk group. The treatment involves surgical resection of the lesions. If the total number of lesions is less than five, introduction of systemic therapy is not mandatory, but if extracutaneous involvement is later diagnosed, chemotherapy must be started. The patients with systemic manifestations should be assigned to the appropriate risk groups, and are treated according to the ALCL-99 protocol [17].

The survival rate in ALCL in comparison to other paediatric malignancies is high, but 20 to 40% of patients suffer from disease relapse [8]. In clinical trials the highest risk of ALCL relapse was observed in the first 12 months after diagnosis, which is consistent with our report [18, 19]. Sixty per cent of relapsing patients are able to achieve a second remission. The second remission is usually achieved due to the chemotherapy based on the Protocol for Relapsed Anaplastic Large Cell Lymphoma of Childhood and Adolescence, which contains among others ICM and ICI blocks of chemotherapy [20]. Due to the presence of therapeutic targets, the relapsing ALCL patients can be treated with ALK-inhibitors (crizotinib) or with anti-CD30 immunotoxin (brentuximab vedotin), but even without remission most relapsing or therapy-resistant patients must undergo allogeneic stem cell trans-

plantation due to potent graft-versus-lymphoma effect [21]. The remission in our patient was achieved with no target treatment.

CONCLUSIONS

Our case report emphasises the fact that different malignancies, ALCL included, can be misdiagnosed as benign skin nodules. Although bacterial infections are the most probable reason for skin infiltrates, in cases of antibiotic therapy failure, patients should undergo more aggressive diagnostics for other causes.

DISCLOSURE

The authors declare no conflict of interest.

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