CASE REPORT

Unusual cause of skin nodules in a child – case report

Michalina Horochowska¹, Jacek Jagiełło², Jadwiga Węcławek-Tompol¹, Marta Rzeszutko³, Anna Zimny², Marek Ussowicz¹, Bernarda Kazanowska¹

¹Department of Paediatric Bone Marrow Transplantation, Oncology, and Haematology, Wroclaw Medical University, Wroclaw, Poland
²Department of General and Interventional Radiology and Neuroradiology, Wroclaw Medical University, Wroclaw, Poland
³Department 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
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 1. Picture of the left forearm. The nodular change with a diameter of 6 cm with an ulceration in the centre

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)
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 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-
ALK is a transmembrane receptor that expresses exclusion leads to a fusion of ALK and nucleophosmin (NPM). NPM-ALK protein is a product of a fusion gene involved in ribosome biogenesis. The NPM-ALK fusion encodes an 80 kD protein, which can localise in cytoplasm as well as in the nucleus of tumour cells. NPM-ALK presence leads to overexpression and constitutional activation of ALK protein domains, resulting in ALK-mediated oncogenesis through uncontrolled proliferation of malignant cells.

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. 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.

C-ALCL presents as a redish skin lesion with ulceration in different parts of the body, which may extend to regional lymph nodes. 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.

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.

The survival rate in ALCL in comparison to other paediatric malignancies is high, but 20 to 40% of patients suffer from disease relapse. In clinical trials the highest risk of ALCL relapse was observed in the first 12 months after diagnosis, which is consistent with our report. 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. 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-

### 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**
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.

REFERENCES

1. Fogelson S, Dohil M. Papular and Nodular Skin Lesions in Children. Semin Plast Surg 2006; 20: 180-191.
2. Hoeger PH. Differential Diagnosis of Skin Nodules and Cysts. In: Harper’s Textbook of Pediatric Dermatology (3rd ed.). Irvine AD, Hoeger PH, Yan AC (eds.). Wiley-Blackwell, Oxford, UK 2011: 92.1-92.9.
3. Hamm H, Höger PH. Skin Tumors in Childhood. Dtsch Arztebl Int 2011; 108: 347.
4. Yang W, Zuo Y, Yang Y, et al. Pediatric anaplastic large cell lymphoma misdiagnosed as multiple organ abscesses: a case report and literature review. Int J Clin Exp Med 2015; 8: 19509-19516.
5. Stevens DL, Bisno AL, Chambers HF, et al. Executive Summary: Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clin Infect Dis 2014; 59: 147-159.
6. Stein H, Mason DY, Gerdès J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985; 66: 848-858.
7. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375-2390.
8. Turner SD, Lamant L, Kenner L, et al. Anaplastic large cell lymphoma in paediatric and young adult patients. Br J Haematol 2016; 173: 560-572.
9. Montes-Mojarro I, Steinhilber J, Bonzheim I, et al. The Pathological Spectrum of Systemic Anaplastic Large Cell Lymphoma (ALCL). Cancers (Basel) 2018; 10: 107.
10. Hsu FY, Johnston PB, Burke KA, Zhao Y. The Expression of CD30 in Anaplastic Large Cell Lymphoma Is Regulated by Nucleophosmin-Anaplastic Lymphoma Kinase-Mediated JunB Level in a Cell Type-Specific Manner. Cancer Res 2006; 66: 9002-9008.
11. Wan W, Albom MS, Lu L, et al. Anaplastic lymphoma kinase activity is essential for the proliferation and survival of anaplastic large-cell lymphoma cells. Blood 2006; 107: 1617-1623.
12. Stein H, Foss HD, Dürkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000; 96: 3681-3695.
13. Li Y-P, Busch RK, Valdez BC, et al. C23 Interacts with B23, A Putative Nucleolar-Localization-Signal-Binding Protein. Eur J Biochem 1996; 237: 153-158.
14. Larose H, Burke GAA, Lowe EJ, et al. From bench to bedside: the past, present and future of therapy for systemic paediatric ALCL, ALK +. Br J Haematol 2019; 185: 1043-1054.
15. Diamantidis MD, Myrou AD. Perils and Pitfalls Regarding Differential Diagnosis and Treatment of Primary Cutaneous Anaplastic Large-Cell Lymphoma. Sci World J 2011; 11: 1048-1055.
16. Kumar S, Pittaluga S, Raffeld M, et al. Primary Cutaneous CD30-Positive Anaplastic Large Cell Lymphoma in Childhood: Report of 4 Cases and Review of the Literature. Pediatr Dev Pathol 2005; 8: 52-60.
17. Van Wering ER, Koning J, Laene-Bruyn E, et al. ALCL 99. International protocol for the treatment of childhood anaplastic large cell lymphoma https://www.skion.nl/workspace/uploads/alcl-99.pdf (accessed 7 July 2019).
18. Mori T, Takimoto T, Katano N, et al. Recurrent childhood anaplastic large cell lymphoma: a retrospective analysis of registered cases in Japan. Br J Haematol 2006; 132: 594-597.
19. Brugières L, Quartier P, Le Deley MC, et al. Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children – a report from the French Society of Pediatric Oncology. Ann Oncol Off J Eur Soc Med Oncol 2000; 11: 53-58.
20. ALCL-Relapse. Treatment protocol for relapsed anaplastic large cell lymphoma of childhood and adolescence. Amended Version II March 2012 https://ptohd.pl/download/alcl-relapse/# (accessed 7 July 2019).
21. Prokoph N, Larose H, Lim M, et al. Treatment Options for Paediatric Anaplastic Large Cell Lymphoma (ALCL): Current Standard and beyond. Cancers (Basel) 2018; 10: 99.