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CASE REPORT

Synchronous neoplasms in a paediatric patient

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ABSTRACT

Cancer is the second leading cause of death in the paediatric population after injuries. 3–10% of them are multiple primary malignant neoplasms, which are a huge problem both in diagnosis and treatment. We present a case of a boy, nearly 2 years old, with synchronous coexistence of T-cell acute lymphoblastic leukaemia and Langerhans cell histiocytosis. During the M AIEOP BFM ALL 2017 Protocol, the patient suffered an injury to the right elbow joint. Despite the limb being provided with a plaster cast and orthopaedic intervention, local improvement was not achieved. The obtained result of the histopathological examination revealed a disseminated aggressive form of histiocytosis affecting the skeletal system and lungs. In the presence of non-specific symptoms for the diagnosed cancer, one should be vigilant and suspect the coexistence of another proliferative process, which may cause no improvement despite proper therapeutic management.

KEY WORDS:
children, acute lymphoblastic leukaemia, synchronous neoplasms, Langerhans-cell histiocytosis.

INTRODUCTION

Paediatric cancers account for approximately 1% of malignant tumours in the general population. They are the second most common cause of death among patients under 18 years of age [1]. The rarity of these diseases in the paediatric population and the different histological structure of neoplasms in children make them a diagnostic and therapeutic challenge. The clinical symptomatology of childhood cancers is often different than in adults; hence, the process of diagnosing a neoplastic disease is sometimes delayed, which adversely affects prognosis [2].

Among all childhood cancers, haematopoietic system cancers are the most common, especially leukaemias (26% of paediatric cancers), followed by central nervous system tumours, lymphomas, and soft tissue cancers [2, 3]. The causes of malignant tumours in children and adolescents are not known, but epidemiological and genetic studies partially explain their origin. The main risk factors include individually specific increased predisposition to cancer, as well as some disease syndromes, such as congenital immunodeficiency, albinism, neurofibromatosis, and genetic syndromes (including Beckwith-Wiedemann, Denys-Drash, Bloom, and von Hippel-Lindau). Chronic inflammatory bowel disease, intestinal polyposis, or other carcinogenic factors predisposing to the development of cancer, mainly in adults (ionising radiation, drugs, viruses) are of lesser importance [4].

An exceptional situation, both among adults and children, is the presence of more than one primary cancer at the same time. The International Agency for Research on Cancer defines multiple primary neoplasm as a neoplasm that develops in its location, is not part of an already existing malignant process, or is not its dissemination, metastasis, or recurrence [5]. Due to the time of development of the next cancer, synchronous cancers can be

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distinguished, in which the second primary cancer develops within 6 months of the first one, and metachronic cancers when this period is longer [5, 6].

The aim of this paper is to present a case of a boy, nearly 2 years old, with T-cell acute lymphoblastic leukaemia (T-ALL) and Langerhans cell histiocytosis (LCH) occurring synchronously.

CASE REPORT

A 22-month-old boy was admitted in September 2021 to the Clinic of Paediatric Haematology, Oncology, and Transplantation of the University Children's Hospital in Lublin with suspicion of a proliferative disease of the haematopoietic system, in order to expand diagnostics and treatment. Respiratory infections in the past month and easy bruising for about 2 weeks had been recorded in the history. The above symptoms were the reason for a visit to the family doctor, who ordered a complete blood count on an outpatient basis. In this examination, thrombocytopaenia of 61 × 10^3/µl and hyperleukocytosis of 285.57 10^3/µl with abnormal smear of white blood cells were found. Undifferentiated cells accounted for 85% of the smear. For this reason, the child was referred to the clinic. At the time of admission to the hospital, the physical examination revealed pallor of the skin with accompanying features of a haemorrhagic diathesis (petechiae and ecchymoses), bilaterally enlarged submandibular lymph nodes, and splenomegaly.

The performed imaging tests showed the following: a wide shadow of the upper mediastinum and slightly increased lung parenchyma in the chest X-ray, splenomegaly in the abdominal cavity ultrasound (84 × 29 mm), and enlarged cervical lymph nodes (22–25 × 12–17 mm) in the neck ultrasound (22–25 × 12–17 mm) hyperechoic cavities. T-cell acute lymphoblastic leukaemia was diagnosed based on the results of the smear and immunophenotypic examination of peripheral blood as well as imaging tests. In the tested peripheral blood sample, 89.6% were T-cell precursor cells. Among them were CD45 (88% dim+), CD7, cytCD3, CD3 (37% dim+), CD1a, CD2, and CD8 cells. No genetic abnormalities were detected. Due to life-threatening hyperleukocytosis, it was decided to start cytoreductive treatment (cyclophosphamide 200 mg/m^2, dexamethasone 5 mg/m^2 for 2 days) before performing a bone marrow aspiration biopsy. 8.52 × 10^3 leukocytes *per* µl were obtained. After the diagnosis, chemotherapy of Protocol I AIEOP-BFM ALL 2017 was started. The response to steroids on day 8 was good (no blasts were observed in the smear). Minimal residual disease on day 15 of treatment in immunophenotypic examination was 0.4% of blasts. On day 33, the blast count was 3%. The boy was treated with the IA-Dexa Protocol, then he continued treatment according to the Regular Protocol IB Part 1 and Part 2. The treatment was complicated by leukoneutropaenia (leukocytes – 0.12 × 10^3/µl, neutrophils – 0.04 × 10^3/µl), anaemia (the lowest haemoglobin concentration – 7.2 g/l), toxic liver damage (ALT – 164 U/l, AST – 69 U/l), and hypertriglyceridaemia (the highest level of TG – 289 mg/dl). In January 2022, chemotherapy, Protocol M, was continued, which was complicated by SARS-CoV-2 infection.

In March 2022, the boy suffered an injury in the area of the right elbow joint. Physical examination after the injury revealed swelling, and pain in the right elbow joint and half of the arm. After an orthopaedic consultation, the limb was fitted with a plaster cast. Due to persistent oedema in the area of the right elbow joint and fever with increasing parameters of inflammation, a joint revision procedure was performed with the collection of material for histopathological examination. An aggressive form of LCH was diagnosed. Histiocytic cells of the granulation tissue showed the presence of CD68/PGM1, S-100 protein, and Cyclin D1. Some of them contained CD1a and, in smaller numbers, Langerin protein. CD30 and ALK-1 were not detected. Molecular alterations such as BRAF were not assessed. Additional tests revealed a mixed population among histiocytes – some with the Langerhans-cell immunophenotype, some with the immunophenotype of xanthogranuloma (CD163+, factor XIII). A positron emission tomography (PET-CT) examination revealed a disseminated neoplastic process, including the anterior mediastinum on the left side, the region of the cranial coronal suture on the right side, the medullary cavity in the proximal part of the shaft of the right humerus, the distal part of the right humerus and the right femur, and the right parietal bone at the frontal suture. It was decided to continue the Protocol II AIEOP-BFM ALL 2017 treatment, with the extension of Dexamethasone reduction as in the Initial Treatment Hemophagocytic Lymphohistiocytosis 2004 Protocol and with strengthening of the therapeutic effect by performing haematopoietic stem cell transplantation (HSCT). Due to the lack of a compatible family donor, it was necessary to search for an unrelated donor. On 15 June 2022, AIEOP BFM ALL 2017 remission maintenance treatment was started.

Despite normal wound healing, elevated inflammatory parameters persisted. Therefore, peripheral blood and swabs from the postoperative wound were collected several times for culture, and the antibiotic therapy was modified. Contrast-enhanced magnetic resonance imaging revealed a massive bone destruction of the distal metaphysis of the right humerus with the presence of extensive irregular oedematous changes of the soft tissues. The progression of lesions in the right elbow area on radiographs (X-ray) and during clinical evaluation is shown in Figure 1.

In June 2022, a follow-up computed tomography scan showed progression of symptoms and probable involvement of the lungs by histiocytosis. On 6 July 2022, at the Department of Surgery, Children's Memorial Health

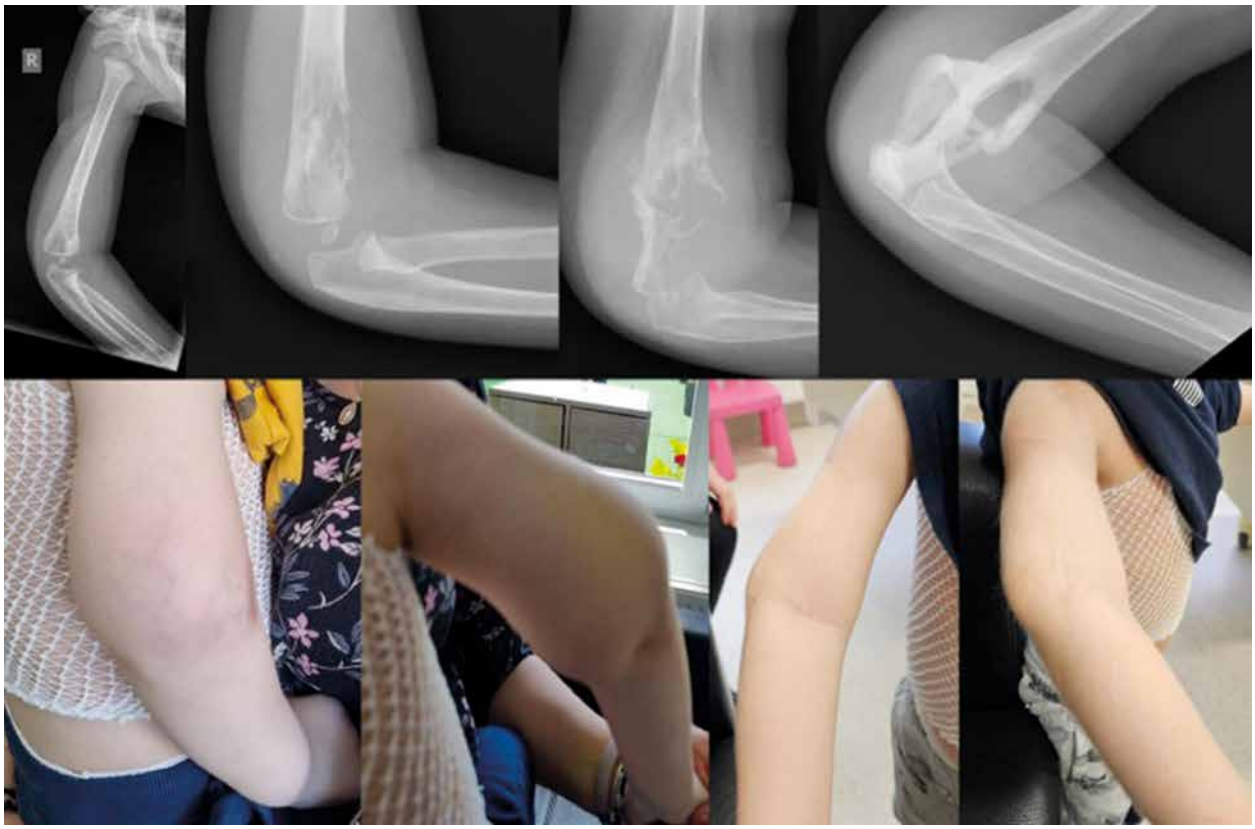

FIGURE 1. Progression of changes radiologically and during clinical examination in the course of histiocytosis in the described patient

Institute, a lung biopsy operation was performed, which confirmed the progression of the disease – the result from the lung biopsy was consistent with the result from the bone. On 20 September 2022, haematopoietic cell transplantation from an unrelated donor (MUD-BMT) was performed. The haematological recovery of the patient was satisfactory: reticulocytes 15.1‰ in the age of +27, leukocytes > 1.0 G/l from +24, granulocytes > 0.5 G/l from +38, platelets > 50,000 from +29, and chimerism on +34 – 98% donor.

Currently, the patient is in remission of both proliferative diseases, which was confirmed by the PET-CT scans in March and the chimerism test in April 2023.

DISCUSSION

T-cell acute lymphoblastic leukaemia accounts for 10–15% of cases of acute lymphoblastic leukaemia, which is the most common malignancy in the paediatric population [7]. It is caused by impaired differentiation, proliferation, and apoptosis of T-cells (CD3+, CD45+, CD2+, CD7+), genetically determined (CDKN2A/2B, NOTCH1, TAL1) and epigenetically. It affects boys 3 times more often, with a median age of onset of 9 years [7]. T-cell acute lymphoblastic leukaemia is most commonly associated with extensive bone marrow involvement, mediastinal tumour, splenomegaly, and central nervous system involvement [7, 8]. The main clinical symptoms of the disease include fever, osteoarticular pain, recurrent infections, and symptoms of bleeding diathesis, as in the present case [8]. Treatment includes chemotherapy, radiotherapy, and HSCT. Overall, 5-year survival is approximately 80%. The risk of recurrence reaches about 25% and is associated with a worse prognosis (30–50%) [7].

Langerhans cell histiocytosis is the most common type of histiocytosis in which Langerhans cells, a type of dendritic cell (CD1a+/CD207+), proliferate and accumulate in excess in specific parts of the body (bone, spleen, lymph nodes, lungs, skin, liver, central nervous system), causing local destruction and stimulating further local lesions [9]. Genetic mutations (*BRAF*, *MAP2K1*, *RAS*, and *ARAF* genes) are considered to be the causative factor of this disease. It occurs in 2–10 *per* million people under the age of 15 years, with a median onset of about 30 months and a slight predominance in male patients [10]. The course of the disease varies from a localised, self-limiting lesion to a disseminated multisystem process with relapses. Bones are most commonly involved (40–80% in the paediatric population), especially as lytic lesions of the cranial vault. Langerhans-cell histiocytosis also affects the ribs, vertebrae, and long bones [11]. In the case of bone manifestation, lytic lesions surrounded by a connective tissue mass with accompanying pain and oedema are most often observed [10, 11]. The described changes, both in terms of localisation as well as the radiological and clinical picture, also occurred in the described patient. In the treatment of LCH, depending on the organ and system involved, chemotherapy, radiotherapy, surgi-

cal treatment, local treatment, or immunotherapy play the most important roles [10]. The overall survival rate is 84–99%, and the risk of recurrence is 10–50%, depending on the extent of the process [10, 12].

A particular problem, not only for paediatric patients, is the synchronous occurrence of 2 or more neoplastic diseases. This not only necessitates modification of treatment, but also reduces the prognosis. Fifteen cases of parallel occurrence of T-ALL and LCH in children are described in the literature, of which 12 cases were diagnosed first with T-ALL, as in the present case, and in 3 cases, LCH was first diagnosed. Langerhans cell histiocytosis was also associated with B-ALL (7 cases), with acute myeloid leukaemia (25 cases), lymphomas (16 cases, equally with Hodgkin's and non-Hodgkin's lymphoma), or solid tumours (44 cases, mainly CNS tumours, neuroblastoma, basal cell carcinoma, retinoblastoma, and bone sarcomas) [13]. Trebo *et al*. noted that the mean age of patients with T-ALL plus histiocytosis was significantly lower than that of patients with T-ALL alone (4.05 ±0.59 vs. 8.82 ±0.14 years), and the baseline leukocyte count was higher in patients with T-ALL and LCH than in the group with T-ALL alone (270.7 ±60.7 × 10^3/μl vs. 134.1 ±5.7 × 10^3/μl). In this study, the time from T-ALL diagnosis to LCH was on average 17.95 months (2.5–33 months) [14]. Similar observations apply to the discussed case – high initial leukocytosis (261.35 × 10^3/μl), lower age of first symptoms (22 months), and 5 months of latency between the diagnosis of both diseases. This necessitates the observation of younger patients with high baseline leukocyte levels for the possible development of histiocytic disorders [14].

Kato *et al*. indicate that the possible mechanism of joint induction of LCH and T-ALL involves disturbances in signalling pathways conditioning cell differentiation and proliferation as a result of mutations within the *RAS* and *CDKN2A* genes [15]. Moreover, Yokokawa *et al*. suggested that T-ALL and LCH tumour cells originate from a common precursor with rearrangement within the *TCR* gene and mutation in the *NOTCH1* gene [16]. Likewise, a study by Rodig *et al*. suggests that activating NOTCH1 mutations may be unique to aggressive Langerhans cell tumours preceded by T-ALL [17].

Yohe *et al*. detail several mechanisms that may explain LC proliferation associated with primary haematological malignancy, including T-ALL. These include the theory of a clonally related process in which LCs originate either from a common stem cell or as a result of myeloid tumour transformation. The "myeloid-based" model of haematopoiesis recognises the maintenance of myeloid potential even as lineage branches toward T- and B-cells. T- and B-cell progenitors are expected to arise from common myelolymphoid progenitors through the myeloid-T and myeloid-B stages [18]. Additionally, Wada *et al*. provided evidence of the presence of progenitor cells in the adult thymus, which have lost the potential to produce B lymphocytes but still have significant potential for macrophages, T lymphocytes, NK cells, and dendritic cells [19]. These observations would support a clonal relationship between the 2 tumours.

CONCLUSIONS

The coexistence of 2 primary neoplastic diseases is a rare and diagnostically difficult phenomenon that affects the treatment process and the patient's prognosis. In the presence of symptoms that are not specific for the diagnosed cancer and no improvement with properly administered treatment, one should be vigilant and suspect the coexistence of another neoplastic process that may require modification of the therapy.

DISCLOSURE

The authors declare no conflict of interest.

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