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CASE STUDY

DIAGNOSTIC DIFFICULTIES IN ALK+ ANAPLASTIC LARGE T-CELL LYMPHOMA IN CHILDREN

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ABSTRACT

Introduction. Lymphomas account for about 12% of malignant tumors in children, and anaplastic lymphoma for 10–20% of Hodgkin's and non-Hodgkin's lymphomas. Clinical symptoms associated with malignant tumors of the lymphatic system are not specific. Diagnosis of these tumors is particularly difficult in the absence of a visible tumor or enlarged peripheral lymph nodes, especially when the symptoms may suggest other, far more common diseases such as infections. Extensive clinical diagnostic procedures, including the exploratory laparotomy, intensive symptomatic treatment and antibiotic therapy do not explain the nature of the disease, do not improve the condition of a patient and lead to the death of sick children. In these cases only an autopsy and histopathological examinations demonstrate the presence of anaplastic large T-cell lymphoma's infiltrates of internal organs, bone marrow and lymph nodes.

Aim. The aim of this study was to demonstrate that in the diseases of children in which it is difficult to establish a definite clinical diagnosis and an intensive antibiotic therapy does not cause any improvement, a neoplastic disease should be always taken into consideration.

Materials and methods. Analysis of the histo-clinical picture of a disease of a child who died due to ALK+ anaplastic large T-cell lymphoma. Diagnostic difficulties resulted in not establishing a clinical diagnosis. Despite conservative treatment, surgical procedure and an intensive antibiotic therapy, the death occurred. The diagnosis was established post-mortem on the basis of immunohistochemical tests: LCA, CD30, CD43, Granzyme B, ALK, CD20, CD3, MPO and Ki67.

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Case study and results. A 14-year-old boy went to the doctor because of abdominal pain and fever. After week-long treatment with antibiotic (Duomox, Astellas Pharma) acute symptoms subsided, but then relapsed after a month and the boy was admitted to the surgery department. Biochemical studies showed increased levels of inflammatory process markers and aminotransferases. Physical examination revealed positive peritoneal signs. With the suspicion of acute Meckel's diverticulitis, laparotomy and appendectomy were performed. During the surgery, a significantly enlarged right lobe of liver was found. Antibiotic treatment was administered and after a few days following the surgery the symptoms subsided. On the 5th day after the surgery the patient's condition deteriorated and on the 8th day he died. The diagnosis was established on the basis of autopsy: ALK+ anaplastic large T-cell lymphoma (LCA+, CD30+, CD43+, ALK+, Granzyme B+, Ki67+ in 85% of cells).
Discussion and Conclusions. Cooperation and efficient communication between the clinician and pathologist are important and necessary in all cases when it is difficult to establish a correct and rapid diagnosis. If in an inflammatory disease the patient's condition is deteriorating despite an intensive antibiotic therapy, the neoplastic disease should be always taken into consideration and the diagnostics should focus on searching for a tumor.

Key words: anaplastic lymphoma, large T-cell, ALK+, children.

INTRODUCTION

Malignant tumors of childhood account for approximately 2% of all neoplasms; however in the 0–15 age group, tumors are the main cause of deaths, followed by accidents and poisonings [5, 9]. The most common malignancies in childhood are the non-epithelial malignant tumors derived from the hematopoietic and nervous systems and from the soft tissues. Non-Hodgkin's and Hodgkin's lymphomas account for about 12% of malignant tumors in children [13, 16–18, 23]. Anaplastic large T-cell lymphoma (ALCL) represents 10–20% of Hodgkin's and non-Hodgkin's lymphomas in childhood [7, 13]. ALCL prevails in the 10–14 age group with the male predominance (ratio M : F is as 3–6 : 1) [10, 22]. It was first described in 1985, belongs to a heterogeneous group of anaplastic lymphomas made up of cells showing the cytokine receptor CD30 expression. About 60% of ALCL [2, 3, 6] show a positive immunohistochemical reaction to the presence of anaplastic lymphoma kinase (ALK) – the product of a gene resulting from a chromosomal translocation t(2;5)(p23;q35) on chromosome 2 [4]. In 85% of ALCL cases ALK is linked to the nucleophosmin (NPM–ALK). In the WHO classification (2008) two types: ALK + ALCL, showing ALK expression (in the cytoplasm and nucleus – NPM–ALK, or in the cytoplasm solely – ALK) and ALK–ALCL**,** were isolated as two new disease units. ALK–ALCL

does not show ALK expression, but it also occurs in the 6th and 7th decade of life and is characterized by a worse prognosis as compared to ALK + ALCL [1, 8, 15, 25, 26]. ALK+ALCL is derived from the activated mature cytotoxic T-lymphocytes [11]. The most common form of tumor is characterized morphologically by the presence of large, pleomorphic cells with relatively abundant cytoplasm and eccentrically located, kidney-shaped nuclei, with distinct nucleoli.

There are also lymphohistiocytic variants, from small cells, and Hodgkin-like variants [2, 4, 19, 20]. In the case of primarily systemic ALCL, the lymph nodes as well as other organs, particularly: skin, bones, also soft tissues, lungs, liver, can be involved [5, 19, 20]. There are also known cases of primarily central nervous system ALCL in children, although they are extremely rare [14]. At the time of ALCL diagnosis most of patients (about 70%) present the III and IV stages of the disease. Peripheral lymph nodes involvement and tumor infiltrations of different tissues and organs are present [10, 12, 26]. General symptoms arising in the course of lymphoma are nonspecific and may significantly precede its clinical manifestation. High fever occurs in 75% of cases. Other symptoms include: night sweats, weight loss, itchy skin [12, 21, 22, 24].

AIM

The aim of this study is to demonstrate that in the disease of children in which it is difficult to establish a definite clinical diagnosis and an intensive antibiotic therapy does not cause any improvement, a neoplastic disease should be always taken into consideration.

MATERIALS AND METHODS

Analysis of the histo-clinical picture of the disease of a child who died due to ALK+ anaplastic large T-cell lymphoma. Diagnostic difficulties resulted in not establishing a clinical diagnosis. Despite conservative treatment, surgical procedure and an intensive antibiotic therapy, the death occurred. The diagnosis was established postmortem on the basis of immunohistochemical tests: LCA, CD30, CD43, Granzyme B, ALK, CD20, CD3, MPO and Ki67.

CASE STUDY AND RESULTS

A 14-year-old boy went to the doctor because of abdominal pain and fever. After a week--long treatment with antibiotic (Duomox) acute symptoms subsided, but then relapsed after a month and the boy was admitted to the surgery department. Biochemical studies showed increased levels of inflammatory process markers and aminotransferases.

Physical examination revealed positive peritoneal signs. With the suspicion of acute Meckel's diverticulitis, laparotomy was performed. During the surgery, a significantly enlarged right lobe of liver was found. An appendectomy was performed, antibiotic treatment was administered and after a few days following the surgery the condition of the patient slightly improved. On the 5th day after the surgery, body temperature increased above 39°C, which was accompanied by limb pain in distal parts. The patient was transferred from the surgical department to the department of pediatrics, in a medium-severe general condition. Imaging diagnostics was performed revealing a tumor-like enlargement of the right lobe of liver. Treatment implemented: intensive antibiotic therapy, plasma transfusion, symptomatic treatment. Despite the treatment the condition of the patient deteriorated. On the 8th day of stay in the department of pediatrics the patient died. Diagnosed with sepsis and a disseminated neoplastic process, the body was sent to post-mortem investigation.

Autopsy revealed: tumor-like enlargement of liver (2 kg) with clearly increased consistency, pneumonia.

Microscopically: tumor infiltrations of lungs, liver, pancreas, stomach, kidneys, spleen, abdominal and mediastinal lymph nodes and bone marrow. In the vessels: tumor embolism. Tumor cells were large, pleomorphic with abundant cytoplasm, eccentrically located nuclei and multiple mitotic figures. Moreover, pneumonia, adult hyaline membrane syndrome, and myocarditis were found.

Immunohistochemical (IHC) tests were performed: LCA, CD30, CD43, ALK, CD20, CD3, Granzyme B, MPO and Ki67. The neoplastic cells showed the expression of LCA, CD30, CD43, ALK, Granzyme B, Ki67 in 85% of the cells. Based on the morphological characteristics and immunohistochemical tests, the diagnosis was established: ALK+ anaplastic large T-cell lymphoma (Fig. 1–8).

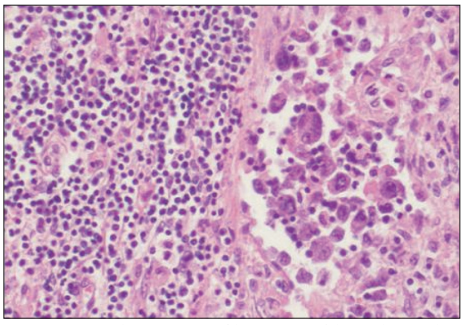

Fig. 1. Neoplasmatic infiltration of lymphonodus [HE 100×]

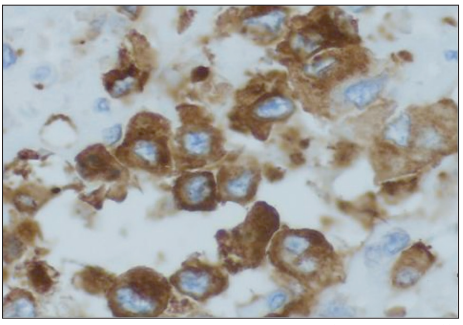

Fig. 2. CD30. Reaction in neoplasmatic cells [Magn. 200×]

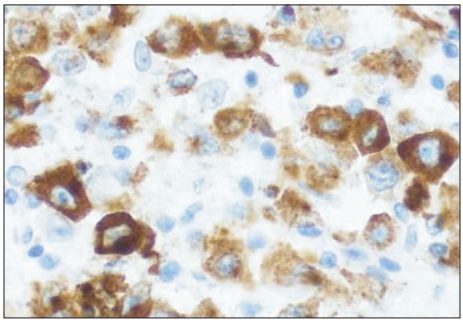

Fig. 3. Granzyme B. Reaction in neoplasmatic cells [Magn. 200×]

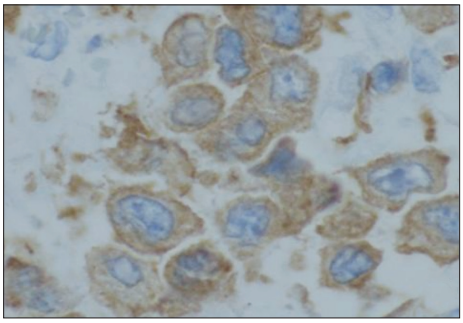

Fig. 4. ALK+. Reaction in neoplasmatic cells [Magn. 400×]

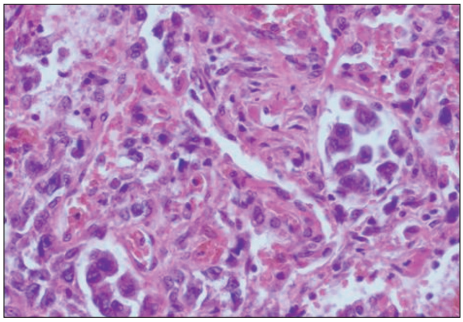

Fig. 5. Neoplasmatic infiltration of the lung [Magn. 200×]

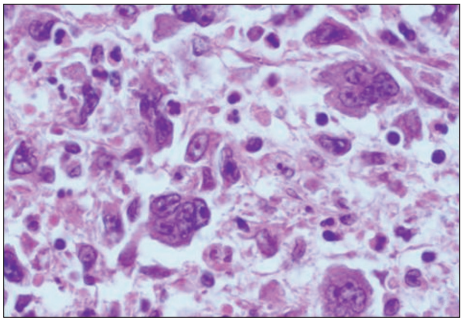

Fig. 6. Neoplasmatic infiltration of the spleen [Magn. 200×]

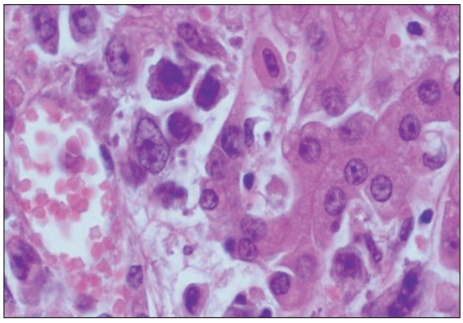

Fig. 7. Neoplasmatic infiltration of the liver [Magn. 200×]

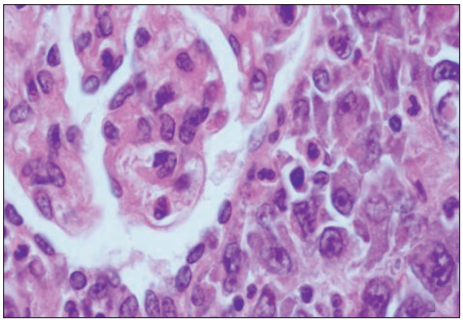

Fig. 8. Neoplasmatic infiltration of the kidney [Magn. 200×]

DISCUSSION

The observed boy was 14 years old. Therefore, he belonged to an age group in which ALCL predominates, as observed by other authors [10, 22]. Establishing a diagnosis post-mortem was possible based on the morphological characteristics and IHC tests

of specimens. The results were in line with the observations of other authors involved in the differential diagnosis of lymphomas in children, who point out diagnostic difficulties [2–4, 6]. Tumor infiltrations, observed by us, were made up of large pleomorphic cells with relatively abundant cytoplasm, eccentrically located nuclei, distinct nucleoli, and reflect the pictures described in literature [2, 4, 19, 20]. Contrary to most frequently described clinical pictures of this neoplasm, in our case there was no enlargement of peripheral lymph nodes [5, 19, 20]. But, similarly to other authors' descriptions, the general symptoms, i.e. weakness and fever, were typical of lymphatic system tumors and could have preceded clinical manifestations [10, 12, 26]. The whole clinical course could have been confusing. Therefore, establishing the correct diagnosis during the child's life was difficult.

CONCLUSIONS

1. In the diagnosis of anaplastic large T-cell lymphoma, ALK+, the immunohistochemical tests of specimens from tumor infiltrates are crucial.
2. At the time of ALCL diagnosis, III–IV stages of the disease are prognostically unfavorable.
3. If in an inflammatory disease the patient's condition is deteriorating despite an intensive antibiotic therapy, the neoplastic disease should be always taken into consideration and the diagnostics should focus on searching for tumor.
4. Cooperation and efficient communication between the clinician and pathologist are important and necessary in all cases when it is difficult to establish a correct and rapid diagnosis.

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