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## **Autoimmune hemolytic anemia and pediatric Hodgkin lymphoma: a clinical case**

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Autoimmune hemolytic anemia (AIHA) in combination with Hodgkin lymphoma (HL) is a rare occurrence in pediatric practice. AIHA can pose significant diagnostic challenges, masking or diverting clinical attention from the underlying oncological process.

**Clinical case.** This article presents a case of an 11-year-old boy diagnosed with both AIHA and HL. Initially, the patient was diagnosed with AIHA; however, further evaluation revealed the presence of HL. Standard therapy for AIHA proved to be ineffective, necessitating a change in treatment strategy. Sustained remission was achieved only after protocol-based combination chemotherapy targeting the primary oncological disease. The article also includes a review of current scientific literature regarding the coexistence of AIHA and HL. Analysis of published clinical cases helps to better understand the pathogenetic mechanisms, diagnostic difficulties, and therapeutic approaches in such rare presentations.

**Conclusions.** This case emphasizes the importance of early recognition of the oncohematological nature of AIHA in pediatric patients. Further research is needed to improve our understanding of the immunopathogenesis of AIHA in the context of HL, which will support the development of better treatment strategies and improve patient outcomes.

The study was carried out according to the principles of the Declaration of Helsinki. Agreement of parents was obtained for the study.

Authors declare no conflict of interest.

**Keywords:** autoimmune hemolytic anemia, Hodgkin lymphoma, children, case report, autoimmune mechanisms, oncohematology.

### **Аутоімунна гемолітична анемія та лімфома Годжкіна у дітей: клінічний випадок**

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Аутоімунна гемолітична анемія (АІГА) у поєднанні з лімфомаю Ходжкіна (ЛХ) – це рідкісне поєднання в педіатричній практиці. АІГА може створювати суттєві діагностичні труднощі, маскуючи або зміщуючи клінічний фокус від основного онкологічного процесу.

Представлено огляд сучасної наукової літератури, присвяченої поєднанню АІГА та ЛХ.

**Клінічний випадок.** Представлено випадок 11-річного хлопчика з поєднанням АІГА та ЛХ. Початково в пацієнта діагностували АІГА, однак подальше обстеження виявило наявність лімфоми Ходжкіна. Стандартна терапія АІГА виявилася малоефективною, що вимагало корекції лікувальної тактики. Стійкої ремісії було досягнуто лише після проведення протокольної комбінованої хіміотерапії, спрямованої на лікування основного онкологічного захворювання. Аналіз опублікованих клінічних випадків дає змогу краще зрозуміти патогенетичні механізми, діагностичні труднощі та терапевтичні підходи за таких рідкісних проявів захворювання.

**Висновки.** Представлений випадок підкреслює важливість раннього розпізнавання онкогематологічної природи АІГА у дітей. Подальші дослідження необхідні для кращого розуміння імунопатогенезу АІГА при ЛХ, що сприятиме вдосконаленню терапевтичних підходів і покращенню прогнозу.

Дослідження виконано відповідно до Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфлікту інтересів.

**Ключові слова:** аутоімунна гемолітична анемія, лімфома Ходжкіна, діти, клінічний випадок, аутоімунні механізми, онкогематологія.

## **Introduction**

**H**odgkin's lymphoma (HL) is one of the most common forms of lymphoma in children and adolescents, accounting for approximately 6.5% of all malignancies in this age group. The highest incidence is observed among adolescents aged 15–19 years, reaching 31.2 cases per 1 million per year. Thanks to modern methods of chemotherapy and radiotherapy, the five-year survival rate of patients with HL exceeds 90% [14]. Timely diagnosis of HL in children plays a critical role, since early detection of the disease allows for rapid initiation of treatment and significantly increases the chances of complete recovery [22].

The relationship between HL and autoimmunity can be viewed as a “two-way street» mechanism, in which autoimmune disorders can promote tumor development. In contrast, lymphoma itself has the potential to induce autoimmune responses through immune dysregulation. Such a combination may serve as a paraneoplastic phenomenon or a complication of the underlying disease, requiring special clinical attention from physicians. The mechanisms of the development of autoimmune hemolytic anemia (AIHA) in HL are not fully understood. It is assumed that tumor cells can produce autoantibodies or cause immune reactions that cross-reactivity with erythrocyte antigens [1,8,10].

AIHA is more commonly described in lymphoproliferative diseases in adults, particularly chronic lymphocytic leukemia (5–10%) and non-Hodgkin lymphoma (2–3%) [23]. However, its occurrence in HL is extremely rare [15]. The association of AIHA with HL in childhood is considered atypical, and only isolated cases of such a combination have been described in the literature [7,12,18].

This publication presents a rare pediatric case of the combination of HL and AIHA, and also discusses possible pathogenetic mechanisms, diagnostic challenges, and therapeutic approaches.

### Clinical case

A boy of 11 years old was admitted to the doctor with weakness, nausea, vomiting, icteric sclerae, and pale skin. On initial examination, it was found that the patient had pale skin with icterus, cervical lymph nodes on the left 1.0×1.5 cm, liver enlargement up to +4 cm, and spleen enlargement up to +2 cm. From the anamnesis, it is known that enlargement of lymph nodes was noted at the age of 9 years. He was observed by a pediatrician with reactive lymphadenopathy of the neck on the background of recurrent nasopharyngitis.

According to the laboratory tests: severe anemia (43g/l), leukopenia ( $2.0 \times 10^9/l$ ), erythrocyte sedimentation rate (ESR) acceleration up to 85 mm/h, hyperbilirubinemia up to 67  $\mu\text{mol/l}$  (indirect 52  $\mu\text{mol/L}$ ), increased C-reactive protein up to 71mg/l. He was referred to the hematology department for further treatment, and a transfusion of B(III)Rh+ (positive) red blood cell mass was performed.

While examination in the hematology department, the results of the lab test were: hemoglobin – 57 g/L, erythrocytes –  $1.83 \times 10^{12}/L$ , color index – 0.93, reticulocytes – 22%, leukocytes –  $2.4 \times 10^9/L$ , platelets –  $277 \times 10^9/L$ , metamyelocytes – 2%, stabs – 12%, segmented neutrophils – 44%, eosinophils – 1%, lymphocytes – 36%, monocytes – 5%, ESR – 48 mm/h, normoblasts – 2 per 100 leukocytes, toxic granulation of neutrophils: Grade 1, total bilirubin – 67  $\mu\text{mol/l}$  (indirect – 52  $\mu\text{mol/l}$ ), C-reactive protein 24 mg/l, direct Coombs test – 4+.

Based on the clinical data and laboratory tests, a diagnosis of AIHA was established. Steroid treatment was initiated with Solu-Medrol 500 mg/day No. 4, ursodeoxycholic acid, and washed red blood cells transfusion. In the background of the treatment, the condition briefly improved, the hemoglo-

bin level rose to 95 g/l in dynamics, and the bilirubin level normalized (22  $\mu\text{mol/l}$ ). However, despite intensive treatment for 2 months, including pulse therapy with Solu-medrol (500 mg/day), taking prednisolone up to 2 mg/kg/day with a subsequent dose reduction, taking rituximab (375 mg/m<sup>2</sup> weekly for up to 4 injections), a stable clinical effect was not achieved. Despite temporary improvement, hemoglobin levels again critically decreased, and bilirubin levels increased. The direct Coombs test remained positive (4+) for a long time, indicating the persistence of an active autoimmune process.

Against the background of AIHA treatment, severe enlargement in the conglomerate of cervical lymph nodes on the left, measuring from 10×5 mm to 30×18 mm, was noted. So, a cervical lymph node biopsy on the left was performed. According to the results of the histological examination of the biopsy, a diagnosis of HL, mixed-cell variant, was established. Immunohistochemical study: cluster of differentiation CD30 – diagnostic expression by cells; CD20 – expression by lymphoid cells; CD3 – expression by lymphoid cells; CD15 – diagnostic expression by cells; multiple myeloma oncogene 1 (MUM-1) – diagnostic expression by cells; paired box 5 (PAX-5) – diagnostic expression by cells; anaplastic lymphoma kinase (ALK) – expression not determined.

According to computed tomography (CT), pathological lymph nodes in the left neck (in the upper, middle, and lower jugular regions), in the posterior cervical region, and the left subclavian region, conglomerates of pathological lymph nodes measuring 54×38 mm are determined. These conglomerates are closely adjacent to the left internal jugular vein and the left common carotid artery – the contrast of the arteries is preserved. The described lymph nodes do not have signs of necrosis. Enlarged lymph nodes in other parts of the neck, in the mediastinum, bronchopulmonary zones, in the right supra- and subclavian, axillary regions, as well as in the abdominal cavity, retroperitoneal space, pelvis, and inguinal regions, are not determined. The spleen has a vertical size of 111 mm, without volumetric formations. The liver has a craniocaudal size (at the level of the right lobe) of 145 mm. There are no volumetric formations in the liver parenchyma.

Taking into account these data, a clinical diagnosis of Hodgkin lymphoma, mixed-cell variant, with involvement of the upper, middle, and lower jugular, posterior cervical, and subclavian lymph

CLINICAL CASE

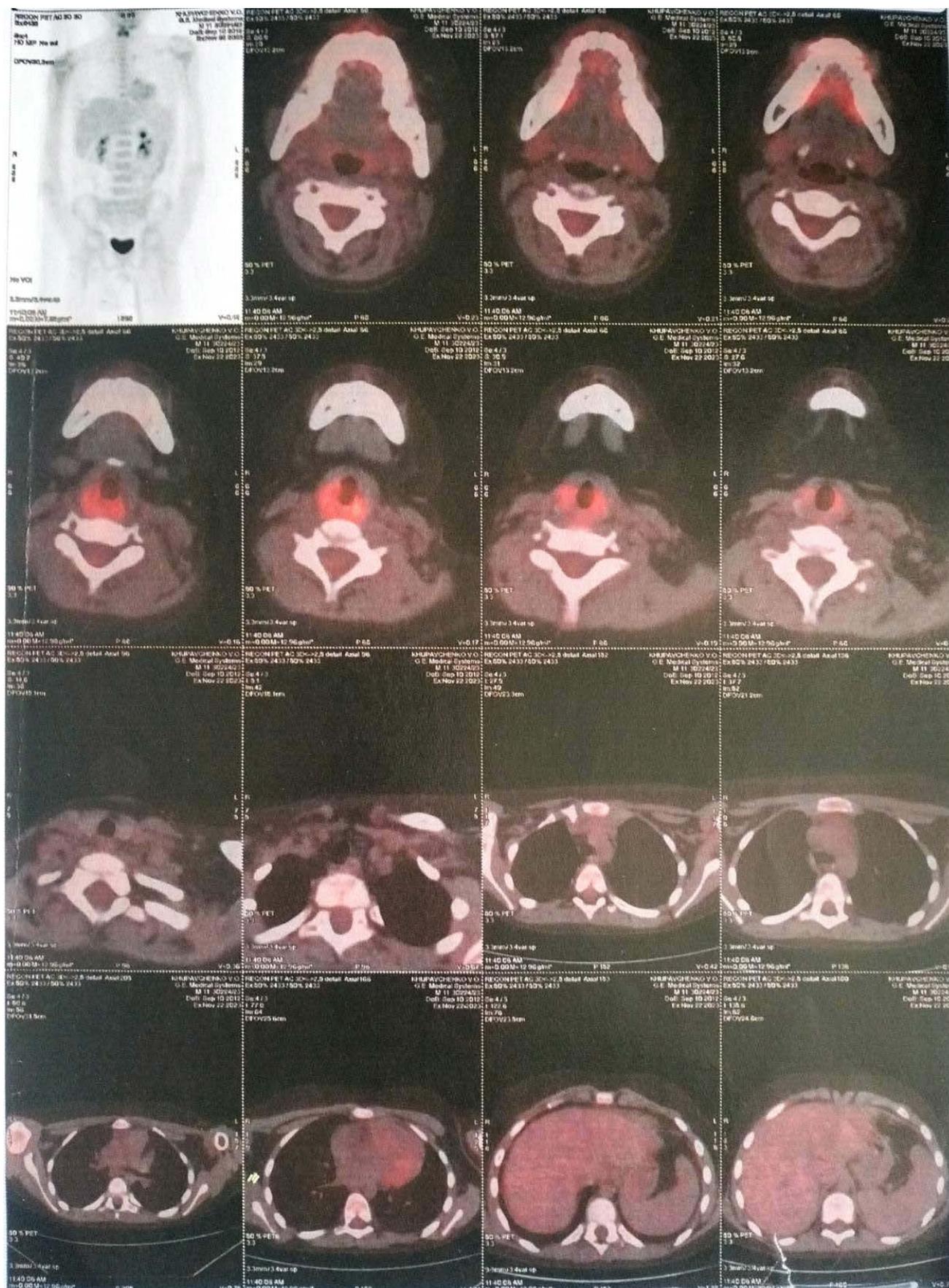


Fig. PET-CT scan of a patient after the second block OEPA

nodes on the left, stage IIB, with autoimmune hemolytic anemia was established.

According to the myelogram, the histological picture suggests secondary myelodysplastic changes. Immunohistochemical study data exclude bone marrow involvement by HL (immunohistochemical study – CD 61 – positive in megakaryocytes; CD 30 – positive cells are not detected).

Chemotherapy EuroNet-Paediatric Hodgkin's Lymphoma Group (EuroNet-PHL) treatment was initiated, against which a decrease in AIHA manifestations was noted. After chemotherapy block first OEPA (Vincristine, Etoposide, Prednisolone, Doxorubicin), the Coombs test was 1+. After chemotherapy block second OEPA, the Coombs test was negative.

According to the results of positron emission computed tomography PET-CT (Fig.1) after the second block, on the left are visualized the upper, middle, and lower jugular lymph nodes, deep cervical lymph nodes, supraclavicular and lower cervical lymph nodes of low intensity fluorodeoxyglucose (FDG) activity, standardized uptake value (SUV) max=1.1, metabolic size up to 8.4×9.9 mm. On the left are visualized single subclavian lymph nodes, with a size of up to 6.9×7.1 mm. Conclusion: signs of pathological accumulation of FDG in the cervical and supraclavicular lymph nodes on the left, which corresponds to a lymphoproliferative process with insignificant metabolic activity, below the mediastinal pool. Increased fixation of contrast in the skeleton's bones is most likely due to a history of autoimmune hemolytic anemia.

Further treatment included two chemotherapy blocks of COPDAC (Cyclophosphamide, Vincristine, Prednisolone, Dacarbazine), after which, according to CT, positive dynamics were obtained in comparison with the previous study, a significant reduction in all pathological lymph nodes, and a decrease in the size of the liver and spleen was noted. The sum of the products of the sizes of the target lymph nodes is 90% reduction and corresponds to a partial good response (PR)/complete response (CR). The child will be referred for radiotherapy.

At this time, the patient has completed chemotherapy and radiation therapy. Positive dynamics were obtained, as in the course of the primary oncological disease, with a significant reduction in all pathological lymph nodes, a decrease in the size of the liver and spleen, as well as regression of clinical manifestations of AIHA, normalization of the

Coombs test. The child is in remission and has regular check-ups in the hematological department.

## Discussion

The described clinical case is an exceptionally rare AIHA and HL in pediatric practice, which gives it special clinical significance. Such a combination creates serious diagnostic difficulties, since immunohematological pathology can mask or shift the clinical focus from the primary oncological process.

In the presented case, we cannot state with complete certainty that AIHA was the primary manifestation of HL. The history showed an increase in lymph nodes, which could be the initial manifestation of the gradual development of the oncological process, but it was regarded as reactive lymphadenopathy. This decision was based on the presence of concomitant chronic nasopharyngeal infection and the absence of progression of lymphadenopathy in dynamics for two years.

According to the literature data, AIHA can develop in lymphoproliferative diseases such as chronic lymphocytic leukemia (5–10%) and non-Hodgkin lymphomas (2–3%), but it is rare in HL [23]. According to one German retrospective study, the frequency of AIHA in patients with HL is only 0.2% [15].

Bowdler and Glick first described the association of AIHA and HL in 1966 [2]. The literature has relatively extensive case reports of AIHA in lymphoproliferative diseases such as autoimmune lymphoproliferative syndrome, chronic lymphocytic leukemia, non-Hodgkin lymphomas, and Hodgkin disease (HL) in adults [5,6,17,20].

Available, albeit limited, review data indicate that AIHA is more frequently associated with late stages of HL (III-IV), especially in nodular sclerosing and mixed cell histological variants [3,13,19,21].

M. Dimou et al. also identified specific demographic and laboratory characteristics that correlated with the development of AIHA: older age, male gender, increased reticulocyte count, high ESR, and decreased absolute lymphocyte count [4].

In a retrospective study by Levine et al. of 71 adult patients with Hodgkin's disease, a positive direct Coombs test was found in seven cases with progressive disease. In three cases, the test was positive at the time of initial diagnosis, and in the others, at the time of relapse [12].

The association of AIHA with HL in children is atypical. Only isolated cases of such a combination

in children and young adults have been described in the literature. In 2021, a case of a 19-year-old patient with HL, Mixed Cellularity subtype, stage IVB, associated with AIHA and lymphopenia was described. He was treated with standard chemotherapy, and he achieved a complete remission [7]. In 2024, a case of an 11-year-old boy with AIHA was published, who was subsequently diagnosed with HL, lymphocyte-depleted type (stage III). After the start of chemotherapy according to the OEPA protocol, a significant improvement in clinical condition and normalization of hemoglobin were observed [18]. In both cases (patients 11 and 19 years old), AIHA preceded the diagnosis of HL, as in our case. AIHA potentially served as a paraneoplastic syndrome, allowing it to be considered as a «red flag» for further investigation in unexplained hemolytic anemia and lack of response to treatment.

Also, in 2016, a 4-year-old girl with mixed-cell type HL (stage III B) was reported, in which, seven years later, against the background of relapse, AIHA developed. This indicates immune destabilization associated with the oncological process. Chemotherapy and steroid treatment led to a rapid and stable remission [9]

The limited reports available on AIHA in the setting of Hodgkin's disease indicate a potential worsening of the prognosis. Still, it is not excluded that this is mainly associated with the typical late stage of the oncological process itself, not with AIHA per se [17].

Several pathophysiological mechanisms explain AIHA and HL's rare but clinically significant association. In most cases, the main mediator of hemolysis is IgG antibodies, but an IgA-mediated form of AIHA has also been described in patients with HL. This condition is often considered a component of a paraneoplastic syndrome in which neoplastic cells produce biologically active substances, such as hormones, cytokines, or abnormal antibodies. Such antibodies can cross-react with red blood cell antigens, initiating autoimmune hemolysis. Interestingly, in most of the described cases, AIHA in the context of HL demonstrates sensitivity to chemotherapy and glucocorticoids, with clinical improvement and normalization of hematological parameters soon after

initiating treatment for the underlying oncological process [1,6,8,10]. The relationship between AIHA and HL remains complex and poorly understood, and further research is critical to better understand the immune mechanisms and develop more effective treatment strategies for this complication.

Corticosteroids are the mainstay of AIHA therapy; however, this first-line regimen is less effective in treating AIHA in HL [4,16]. In one single-center study, the use of rituximab, traditionally a second-line therapy, significantly improved mortality compared with corticosteroids in patients with AIHA and lymphoproliferative disease [16]. In your case, no stable improvement was noted on corticosteroids and rituximab. However, in our case, like in cases in the literature [3,7,18], treatment of the underlying hematologic malignancy with protocol-based combination chemotherapy resulted in effective treatment of AIHA.

### Conclusion

The presented clinical case highlights an exceptionally rare concurrence of AIHA and HL in a pediatric patient, emphasizing its clinical and diagnostic relevance. AIHA poses significant diagnostic challenges, as it can obscure or divert attention from the underlying malignant process. This underscores the necessity for heightened clinical vigilance, a multidisciplinary diagnostic strategy, and thorough longitudinal assessment to ensure early and accurate diagnosis.

Furthermore, the limited efficacy of corticosteroids as the standard first-line therapy for AIHA in cases associated with HL necessitates individualized treatment modifications, including careful tapering strategies. Notably, sustained remission of AIHA is often unachievable without effective treatment of the underlying lymphoma, typically through combination chemotherapy.

This case also highlights the importance of advancing our understanding of the immunopathogenesis of AIHA in the context of HL. Further research is crucial to refine therapeutic approaches, improve patient outcomes, and inform clinical decision-making in similarly complex presentations.

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