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CASE REPORT

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WOMAN WITH TURNER SYNDROME AND HER CHILD WITH ACUTE LEUKEMIA (A CASE REPORT)

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Turner syndrome (TS) is a chromosomal condition that affects development in females. The case of TS in the mother whose child was diagnosed with acute leukemia at the age of 1.5 years is presented. *FANCI* gene in child was detected among 94 genes associated with hematologic malignancies. Acute lymphoblastic leukemia, common-B II, L1, associated with t(12;21)(p13;q22), *TEL/AML1* (*ETV6/RUNX1*) in a child was detected during a prophylactic examination. During the treatment of the baby, the mother had a second pregnancy, which ended in miscarriage at 8 weeks. Upon cytogenetic examination in the mother TS was revealed — mos45,X[23]/46, XX[7], and the father's karyotype was without abnormalities (46, XY). After chemotherapy, the child is in clinical-hematological remission. It could be suggested that chromosomal abnormalities in mother with TS may cause the chromosomal instability and hematological malignancy in offspring.

***Key Words*: Turner syndrome, acute leukemia, phenotype, reproductive history.**

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Turner syndrome (TS) is a chromosomal condition that affects development in females [1, 2]. This pathology is characterized by the absence of the whole second X chromosome or its fragment. TS frequency varies from 1 per 2500 to 1 per 3000 liveborn baby girls [3]. In Ukraine, the TS frequency is 77.5 per 100 000 liveborn baby girls [4]. Most often TS is diagnosed postnatally [5, 6]. Mavridi *et al*. [7] noted that spontaneous pregnancies are rare (5%) in women with TS and are of relatively high risk.

The etiological role in the development of leukemia is played by the genetic features of hematopoiesis [8]. It was noted that various forms of acute and chronic leukemia are often found in individuals with hereditary diseases, accompanied by violations and instability of the genotype [9].

In families with hereditary chromosomal defects, such as trisomy of chromosome 21 (Down syndrome), nondisjunction of sex chromosomes (Klinefelter syndrome, Turner syndrome) [10–13], spontaneous chromosome breaks (Blum syndrome, Fanconi anemia, ataxia telangiectasia, Nijmegen breakage syndrome etc.), a marked increase in cases of acute myeloid leukemia, chronic myeloid leukemia and other cancers has been mentioned [2, 9, 14, 15].

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood age, accounting for 30% of cases of childhood cancer. This disease often manifests with common and nonspecific symptoms. Early diagnosis of ALL is only possible when using a general blood test [16, 17]

There are references to cases of a combination of TS and leukemia in the literature [18, 19]. Cases of leukemia associated with TS are rare, however, they are sometimes diagnosed in the same person [1, 20]. In the available literature, we did not find reports of ALL in offspring of TS. Here we report one case of TS patient including the case of ALL in her child.

In Lviv region (West of Ukraine) a comprehensive study of TS has been conducted [6, 21]. This is the first case in our practice where a mother with TS has a child with cancer. We provided the analysis of the karyotype of the TS in woman whose child was diagnosed with leukemia at the age of 1.5 years. Leukemia in a child was detected during a prophylactic examination, when the child underwent a general blood test at preschool.

***Case presentation*.** The study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The informed consent of the patient included into the study was obtained.

Reproductive history was collected: during the treatment of the baby, the mother had a second pregnancy, which ended in miscarriage at 8 weeks. Since the couple's second pregnancy ended in miscarriage early and her daughter had leukemia, her parents had to be consulted by a geneticist. Cytogenetic examination revealed Turner's syndrome in the mother, the father karyotype being without abnormalities (46, XY). The mother has a karyotype mos45,X[23]/46,XX[7], European appearance, height of 160 cm and weight of 49 kg. In childhood, she did not suffer often from acute respiratory disease, at the age of 5 years she became ill with measles. Age of spontaneous menarche — 15 years, not regular, slightly painful. The phenotype of a mother without features. The variability

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Abbreviations used: ALL – acute lymphoblastic leukemia; TS – Turner syndrome.

of the cytogenetic image is expressed in the variability of the phenotype of patients with TS, which is important in predicting the course of the disease. The first pregnancy, from which the proband was born, flowed without complications, age at pregnancy — 30 years. All tests that she had during this pregnancy were within normal limits. The baby was born from the first full-term pregnancy, body weight at birth was 3200 g. She grew and developed according to age, breastfeeding up to 7.5 months, then consumed adapted mixtures.

Hereditary history: the family has 4 cases of diabetes in the relatives, no consanguineous marriage was observed (Figure). Two congenital anomalies of different organs were observed in the family history of the father: birth defect (insufficiency of mitral valve) had a grandmother proband, and the great-grandfather of the proband missed the right kidney from birth, however, he lived with the defect up to 87 years. Stroke in combination with diabetes was in grandfather by mother's line (died at the age of 76) and in grandmother by father's line (died at the age of 83), and in the uncle at the age of 61 (alive). Grandfather proband on the line of mother had rheumatism at the age of twenty.

In October 2017, the child complained of general malaise. The parents performed a blood test showing an increase in anemia and thrombocytopenia, so they consulted a hematologist. On admission the general condition was severe, hepatomegaly (+2.5 cm); peripheral lymph nodes +1.5 cm.

Laboratory results of the girl aged 1.5 years demonstrated thrombocytopeny (97×10^9/l) with 36% leukemic blasts, severe anemia (HGB — 9.8 g/dl). Blood count: (13.10.2017): RBC — 3.51×10^{12}/l, WBC — 6.7×10^9/l, blasts — 36%, eosinophiles — 1%, bands — 4%, segments — 4%, lymphocytes — 50%, monocytes — 3%, mononuclear cells — 1%, plasma cells — 1%. In myelogram: normocellular bone marrow: blasts — 87.0%, myelocytes — 0%, metamyelocytes — 0%, bands — 0%, segments — 1.2%, mono — 0.8%, lymphocytes — 6.0%, plasma cells — 0%, eosinophiles — 0%, basophiles — 0%, erythroblasts — 2.8%. Cytochemical study of blast cell myeloperoxidase "–" negative, PAS "+" granular.

Immunophenotyping of bone marrow blasts CD2 — 0%, CD3 — 0%, CD4 — 0%, CD5 — 0%, CD7 — 0%, CD8 — 0%, CD19 — 100%, CD20 — 0%, CD22 — 97%, CD10 — 100%, cCD79a — 87%, CD58 — 95%, CD45 — 100%, CD34 — 80%, CD38 — 95%, CD13 — 0%, CD33 — 0%, CD15 — 0%, CD65 — 0%, CD117 — 0%, HLA-DR — 93%, Anti-MPO — 0%, Anti-TdT — 88%.

Molecular genetic study of bone marrow fluorescence *in situ* hybridization and polymerase chain reaction: t(9;22)(q34;q11), *BCR/ABL*; Pattern of hybridization nuc ish 9q34(ABLx2)22q11(BCRx2)[100]; t(1;19)(q23;p13); *E2A/PBX1*, t(4;11)(q21;q23) *AF4/MLL* not found; t(12;21)(p13;q22), *TEL/AML1* (*ETV6/RUNX1*) in 94.0% cells. Pattern of hybridization nuc ish 12p13(ETV6x1,2),21q22(RUNX1x3)(ETV6con

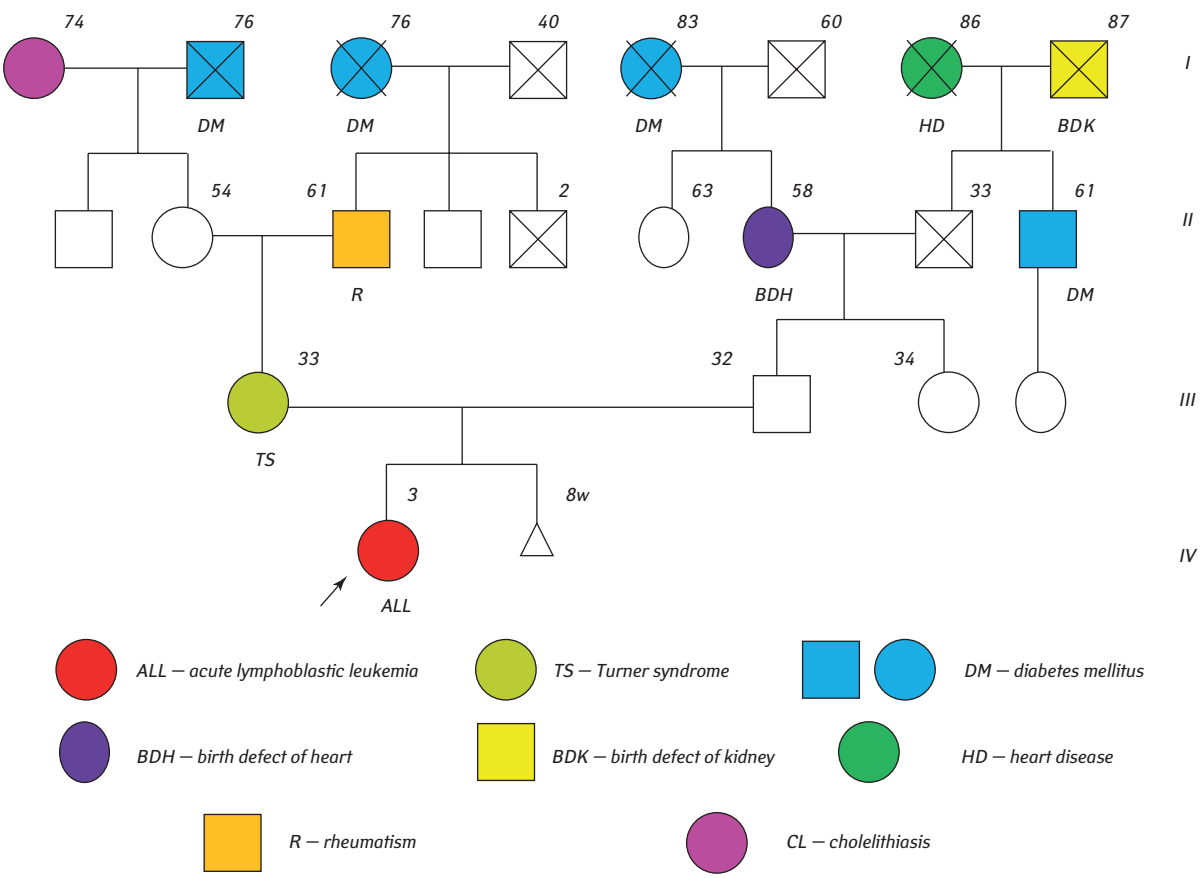

Figure. Family tree of the patient with acute leukemia

RUNX1x1)[94/100]. No increase in chromosome signals 15 and 17 was detected. Pattern of hybridization nuc ish(PMLx2),17q21.1(RARAx2)[100].

Ultrasound: (11/14/17). Liver: Lower edge right lobe +20 mm, left lobe + 60 mm below the costal arch. Parenchyma echogenicity is normal, fine-grained, homogeneous. The stroma of the liver is neither dense nor thickened. The gallbladder is typical, ovoid in shape, not deformed, the walls are neither dense nor thickened, the lumen is homogeneous. The pancreas is clear, not thickened, echogenicity reduced, the structure is homogeneous. The spleen is not enlarged, conventional echostructure, 84 × 28 mm. The kidneys are located typically, the usual size without signs of dilatation. The sinuses are slightly dense. The right split of the excretory system. The bladder wall is not thickened, the contents are acoustically transparent. No pathological lesions were detected in the abdominal cavity.

X-ray chest of thorax, magnetic resonance imaging of the head is normal. Ophthalmologist (11/15/17): fundus is normal. Neurologist (11/14/17): No organic CNS changes detected.

DNA sample was extracted from child blood leucocytes. The sequence analysis and deletion/duplication testing of the 94 genes associated with hematologic malignancies was done by NGS Illumina technology at INVITAE laboratory, USA. The *FANCI* gene in child was detected. A Variant of Uncertain Significance, c.17T>C (p.Leu6Ser), was identified in *FANCI*. The *FANCI* gene is associated with autosomal recessive Fanconi anemia, type I. A Variant of Uncertain Significance, c.2621T>C (p.Ile874Thr), was identified in *FANCM*. The *FANCM* gene is associated with an autosomal recessive condition characterized by an increased risk for malignancy and infertility. Additionally, there is preliminary evidence that *FANCM* is associated with autosomal dominant predisposition to breast cancer and autosomal recessive Fanconi anemia (PMID: 16116422, 19423727, 21681190). The clinical significance of the identified variant is uncertain.

Diagnosis of a child — ALL, common-B II, L1 (FAB), associated with t(12;21)(p13;q22), *TEL/AML1* (ETV6/RUNX1).

Treatment — from 14.11.2017, ALLIC-BFM 2009 chemotherapy was started. The child received chemotherapy for the standard-risk group (protocols I A, IB, mM, II from 14.11.2017 to 26.06.2018, supportive chemotherapy, including intrathecal administration of methotrexate № 6, from 11.07.2018 to 14.11.2019). The patient was prednisone-good responder on day 8 after 7 days of prednisone pre-phase (the absolute blasts count < 1,000/μL in the peripheral blood). The evaluation of minimal residual disease in the bone marrow on day 15 0.08%, on day 33 in bone marrow minimal residual disease 0.0%.

During chemotherapy, the following complications were observed in the child: pancytopenia, acute obstructive tracheobronchitis, nausea and vomiting, enteropathy, stomatitis, alopecia, toxic hepatopathy with transaminase elevation (alanine transaminase and aspartate transaminase 5–7 times), which was caused by forced pauses of chemotherapy.

Also, used in the treatment, antibiotics and modern antimycotics, allopurinol, selective bowel decontamination — nifuroxazide, prevention of pneumocyst preempties — biseptol, inhalation and nebulizer therapy: berodual and pulmicort, intensive infusion postsyndromic therapy, erythro- and thromboconcentrates, intravenous human immunoglobulin etc.

Now patient is in clinical-hematological remission after completing a full course of chemotherapy ALLIC-BFM 2009. In control examinations was minimal residual disease negative, and *TEL/AML* oncogene is not found.

Discussion. TS is characterized by the absence of one complete or partial copy of the X chromosome. To make a diagnosis, a karyotype analysis should be performed in a person who has symptoms suggestive of the disease [3, 22]. It should be remembered that patients with mosaicism would not always present all clinical signs of TS [23]. In our case, the patient had no clinical features of TS. Mosaic girls can be presented with a continuum of clinical features ranging from normal appearance to a typical Turner phenotype [5, 23].

The development of any case of leukemia can be triggered by mainly external factors that induce leukemogenesis, a hereditary predisposition or a combination of both. It could be suggested that chromosomal abnormalities in mother may cause the chromosomal instability in offspring and as the results hematological malignance in the child. The disorders of chromosomal instability associated with the risk of developing certain types of malignancies especially leukemia [9, 13, 14].

Females with TS are presented with streak gonads, consisting of connective tissue and a limited number of follicles. Ovarian failure in TS starts to develop in fetal period. In adolescent and adult life it can be detected by high serum levels of follicle-stimulating and luteinizing hormones, while estradiol levels are usually low. To promote the development of the secondary sex features, the girls with TS require estrogen replacement therapy. It is usually started at age from 12 to 13 years, if no signs of spontaneous puberty appear by this time [3].

The use of modern molecular cytogenetic methods helps to increase the level of medical and genetic counseling and provides the appointment of correct symptomatic treatment for such patients. Particular attention should be paid to women with TS during pregnancy. Their offspring need special monitoring of their health status.

Our case report demonstrated that in mothers with mosaic TS there is a probability of a birth of a child with acute lymphoblastic leukemia. Therefore, it is necessary to carry out the cytogenetic research in parents with children who have been diagnosed with oncohematological disease for medical and genetic coun-

seling of the family and determining the risk of birth of a child with oncohematological pathology. In our case, ALL had a favorable prognosis for a baby born by a mother with TS. The patient was in the standard risk group (standard-risk group ALL) with minimal toxic and adverse reactions to chemotherapy. The child recovered from ALL and is now in clinical-hematological remission. It could be suggested that mother's chromosomal abnormalities may cause the chromosomal instability in offspring, thus resulting in risk of the development of hematological malignancy in the child.

REFERENCES

1. **Siddiqui N, Ali Baig MF, Khan BA.** A case report of acute myelogenous leukemia with Turner syndrome. J Pak Med Assoc 2017; **67**: 1438–40.

2. **Larizza D, Albanesi M, De Silvestri A, *et al.*** Neoplasia in Turner syndrome. The importance of clinical and screening practices during follow-up. Eur J Med Genet 2016; **59**: 269–73.

3. **Gravholt CH, Andersen NH, Conway GS, *et al.*** Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 2017; **177:** G1–70.

4. **Zelinska N, Shevchenko I, Globa E.** Nationwide study of Turner syndrome in Ukrainian children: prevalence, genetic variants and phenotypic features. J Clin Res Pediatr Endocrinol 2018; **10:** 256–63.

5. **Paolucci DG, Bamba V.** Turner Syndrome: care of the patient: birth to late adolescence. PediatrEndocrinol Rev 2017; **14**: 454–61.

6. **Kitsera N, Helner N, Osadchuk Z, *et al.*** Clinical and genetic features of women's cohort with Turner syndrome from Lviv region (West Ukraine) for 1997-2017. J Genome 2018; **1:** 101–5.

7. **Mavridi A, Ntali G, Theodora M, *et al.*** A spontaneous pregnancy in a patient with Turner syndrome with 45,X/47,XXX mosaicism: A case report and review of the literature. J Pediatr Adolesc Gynecol 2018; **31:** 651–4.

8. **Jin MW, Xu SM, An Q, Wang P.** A review of risk factors for childhood leukemia. Eur Rev Med Pharmacol Sci 2016; **20:** 3760–4.

9. **Taylor AMR, Rothblum-Oviatt C, Ellis NA, *et al.*** Chromosome instability syndromes. Nat Rev Dis Primers 2019; **5:** 64.

10. **Ramphul K, Mejias SG, Joynauth J.** Leukemia in Down syndrome children based on national estimates. J Pediatr Hematol Oncol 2019; **41**: 421–2.

11. **Rau RE, Carroll AJ, Heerema NA, *et al.*** Klinefelter syndrome and 47,XYY syndrome in children with B cell acute lymphoblastic leukaemia. Br J Haematol 2017; **179:** 843–6.

12. **Chennuri V, Kashyap R, Tamhankar P, Phadke S.** Chronic myeloid leukemia in case of Klinefelter syndrome. Indian J Hum Genet 2014; **20:** 69–71.

13. **Ji J, Zöller B, Sundquist J, Sundquist K.** Risk of solid tumors and hematological malignancy in persons with Turner and Klinefelter syndromes: A national cohort study. Int J Cancer 2016; **139:** 754–8.

14. **Alter BP.** Fanconi anemia and the development of leukemia. Best Pract Res Clin Haematol 2014; **27:** 214–21.

15. **Aljarad S, Alhamid A, Rahmeh AR, *et al.*** Bloom syndrome with myelodysplastic syndrome that was converted into acute myeloid leukaemia, with new ophthalmologic manifestations: the first report from Syria. Oxf Med Case Reports 2018; **12**: 414–8.

16. **Kaplan JA.** Leukemia in children. Pediatr Rev 2019; **40:** 319–31.

17. **Rehman A, Abbas N, Saba T, *et al.*** Classification of acute lymphoblastic leukemia using deep learning. Microsc Res Tech 2018; **81:** 1310–7.

18. **Saito T, Usui N, Asai O, *et al.*** Toxicity and outcome of intensive chemotherapy for acute lymphoblastic leukemia complicated with Turner's syndrome. Intern Med 2005; **44:** 145–8.

19. **Davidow KA, Walter AW.** Medulloblastoma and secondary acute myeloid leukemia in a patient with Turner syndrome. Pediatr Blood Cancer 2019; **66:** e27576.

20. **Manola KN, Sambani C, Karakasis D, *et al.*** Leukemias associated with Turner syndrome: report of three cases and review of the literature. Leuk Res 2008; **32:** 481–6.

21. **Kitsera N, Helner N, Osadchuk Z, *et al.*** Reproductive anamnesis of women's cohort with Turner syndrome from Lviv region (West Ukraine). J Genet DNA Res 2018, **2:** 110.

22. **Frelich A, Frelich J, Jeż W, Irzyniec T.** Selected clinical features of the head and neck in women with Turner syndrome and the 45,X/46,XY karyotype. Endokrynol Pol 2017; **68:** 47–52.

23. **Noordman ID, van der Velden JA, Timmers HJ, *et al.*** Karyotype — phenotype associations in patients with Turner syndrome. Pediatr Endocrinol Rev 2019; **16:** 431–40.