A rare case of a patient with Rubinstein-Taybi syndrome and acute lymphoblastic leukaemia

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ABSTRACT

Rubinstein-Taybi syndrome (RSTS) is a congenital disorder characterized by intellectual disability and numerous congenital defects of the face and limbs. Its associated mutations can coexist with various cancers. This study presents the case of a 7-year-old girl with RSTS, who was referred to the Emergency Department due to the occurrence of haemorrhagic diathesis in the form of punctate petechiae on the trunk and bloody spots on the upper and lower limbs. The blood count revealed profound anaemia, thrombocytopenia and the presence of atypical cells in the white blood cell smear. The myelogram showed 73% of undifferentiated cells. Based on the results of cytomorphology, immunophenotype and cytogenetic examination, the girl was diagnosed with acute lymphoblastic leukaemia pre B common (+) and treatment was started by the AIEOP-BFM 2017 protocol. The case of this patient is one of the few reports of acute lymphoblastic leukaemia in a patient with RSTS. Analysis of the response to treatment and side effects observed during the therapy of a girl with RSTS may help to individualize and optimize the therapy.

Keywords: acute lymphoblastic leukaemia, child, Rubinstein-Taybi syndrome, cancer predisposition

INTRODUCTION

Rubinstein-Taybi syndrome (RSTS) is a congenital disease, transmitted in an autosomal dominant manner, which was first described in 1957 by Mikhail J. and co-authors as a characteristic bent, clubbed thumb and other accompanying dysmorphic defects of the face and limbs [1, 2]. The incidence of RSTS is estimated at 1:100,000 to 1:125,000 births.

There are no clear diagnostic criteria for many of the symptoms present in patients with RSTS. As a result, it is difficult to establish genotype-phenotype correlations and predispositions to diseases associated with the syndrome [3, 4]. Most often, patients with RSTS have characteristic facial features, enlarged thumbs and halluxes, and short height. More than half of the patients also suffer from microcephaly, and in some cases: cyanotic heart defects, pulmonary hypertension, intellectual disability and other neurological disorders [5].

The cause of RSTS is considered to be heterozygous mutations arising de novo in epigenetic genes in chromosomal regions 16p13.3, where the *CREBBP* gene is located [4]. Studies show that over 60% of RSTS patients have a mutation in the gene encoding the transcription coactivator of CREB-binding protein (CREBBP) [6]. Mutations in the p300 E1A binding protein occur in 10% of RSTS patients. This protein is encoded by the human *EP300* gene, located on chromosome 22q13.2 [4].

In this group of patients, there is no predominance of one type of cancer. Only a few cases of haematologic malignancies in patients with RSTS have been reported in the literature. For this reason, it is difficult to conclude the incidence of blood cancers in people with RSTS [7].

This study aims to present a case report of a patient with Rubinstein-Taybi syndrome, who was diagnosed with acute lymphoblastic leukaemia (ALL) — pre-B common (+). The patient's medical records were analysed in terms of clinical and laboratory data.

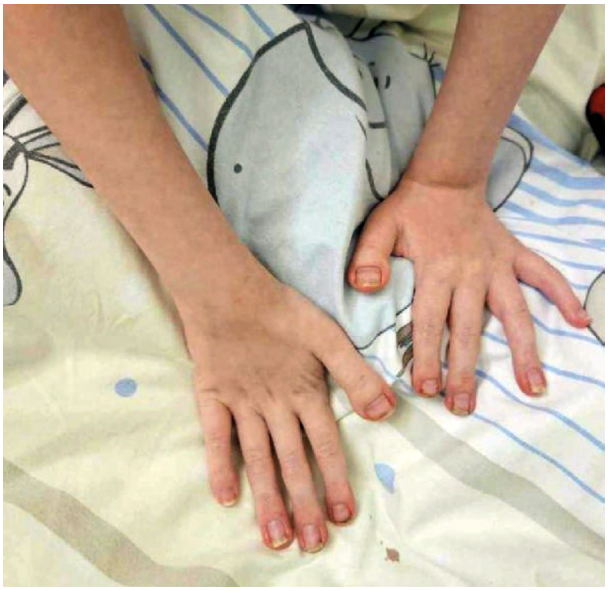

Figure 1. Clinical features of RSTS in a patient. Transverse positioning of the distal phalanges of the hands and wide thumbs

CASE REPORT

A 7-year-old girl with diagnosed Rubinstein-Taybi syndrome was admitted to the Emergency Department due to the occurrence of haemorrhagic diathesis in the form of punctate petechiae on the trunk and bruises on the upper and lower limbs. The blood count revealed profound anaemia, thrombocytopenia and the presence of atypical cells in the white blood cell smear. The white blood cell count (WBC) was 0.0146 G/L, haemoglobin (Hb) 7.3 g/dL, and platelets (PLT) 0.011 G/L. The patient's physical examination revealed a delay in psychomotor development and phenotypic features of the Rubinstein-Taybi syndrome: convex forehead, narrow jaw, deep-set eyes, slanting position of the eyelids, increased mobility of the elbow joints, transverse position of the distal phalanges of the hands and wide thumbs. Particularly noteworthy was a systolic heart murmur with a loudness of 2–3/6 on the Levine scale, which resulted from the presence of a flaccid interatrial septum with a possible trace of leakage at this level, visible in the echocardiographic examination of the heart.

The girl was admitted to the Department of Paediatric Haematology, Oncology and Transplantology with suspicion of a proliferative disease of the haematopoietic system. Bone marrow aspiration biopsy showed 73% undifferentiated cells. Based on cytomorphology, immunophenotype and cytogenetic examination, the girl was diagnosed with acute lymphoblastic leukaemia (ALL) — pre-B common (+). Moreover, cytogenetic analysis showed a hypotriploid female karyotype in 17 metaphase plates 67~68<3n>,XXX-,+X,-1,-7+10,-13,+14,-19,+21,+mar[17]/46,XX.

The girl began chemotherapy according to Protocol I according to the AIEOP-BFM ALL 2017 protocol IAp (International Collaborative Treatment Protocol for Children and Adolescents with Acute Lymphoblastic Leukaemia). The response to prednisone used in cytoreductive prophase on the 8th day of treatment was good (no blasts were detected in the white blood smear), on the 15th day of treatment, the number of blast cells in the myelogram was 2%, and 0.12% of B lymphocyte precursor cells with an abnormal phenotype were observed in the cytometer, corresponding to blast cells at diagnosis. On day 33 of treatment, the blast count was 0% and minimal residual disease was negative. Based on the results, the patient was classified as an intermediate risk group. Due to high pro-thrombotic factors, she required antithrombotic prophylaxis in the form of prophylactic administration of low-molecular-weight heparin.

The treatment was complicated by leukopenia (minimum WBC value: 0.03 G/L), anaemia (Hb 7.0 g/dL), coagulation disorders, and hypertriglyceridemia. The girl required a transfusion of red blood cell concentrate, platelet concentrate and correction of abnormalities in the coagulation system. On day 16 of Protocol I, the patient was observed to have symptoms of septic shock with increasing inflammatory parameters: procalcitonin (PCT) 30.770 ng/mL, C-reactive protein (CRP) 13.69 mg/dL and positive blood culture results (*Klebsiella pneumoniae*). The treatment included broad-spectrum empirical antibiotics, consistent with the results of the antibiogram. The patient's clinical condition and bone marrow regeneration improved. At time point TP-2, before the start of Protocol M, the risk group was updated based on the result of the bone marrow aspiration biopsy. Minimal residual disease was still negative. Chemotherapy was continued by the AIEOP-BFL ALL 2017 POLAND protocol (Consolidation A, Consolidation B, Protocol M, Protocol II). Tolerance of chemotherapy was good. The treatment was complicated by profound aplasia and metabolic disorders (hyperglycaemia, hypertriglyceridemia). The girl required a transfusion of blood and blood products. Currently, the patient is under the care of the Haematology Clinic undergoing treatment to maintain remission.

DISCUSSION

Studies of people with RSTS describe the occurrence of various cancers, most often appearing before adulthood. In a Dutch study of 87 patients diagnosed with RSTS, 8% of patients developed cancer, one of them developing diffuse large B-cell lymphoma (DLBCL) [7, 8]. Only three cases of patients with this syndrome and acute lymphoblastic leukaemia have been described in the literature, including one similar case of a paediatric patient with RSTS and haploid B-cell lymphoblastic leukaemia (B-ALL) [9, 10]. In a study of 25 patients with RSTS, one was diagnosed with early B-cell acute lymphoblastic leukaemia at 10 months of age and underwent allogeneic bone marrow transplantation. An increased incidence of excessive keloid formation is also observed in this syndrome [11].

In the only case report found in the available literature, a 6-year-old patient diagnosed with Rubinstein-Taybi syndrome described symptoms such as bone pain, refusal to walk, fever and enlarged lymph nodes. On admission to the hospital, the patient's blood count showed that the WBC count was 0.0107 G/L, Hb was 6.7 g/dL and PLT was 2 G/l. Bone marrow aspiration biopsy revealed the presence of 95% blast cells. Cytogenetic studies characterized an almost haploid karyotype of 27,X,+X,+14,+18,+21[11] [9]. In the patient described, the symptoms upon admission to the hospital were different: the dominant features were haemorrhagic diathesis — petechiae and bruises, as a manifestation of a reduced number of thrombocytes. However, laboratory tests can similarly observe leucocytosis with the presence of undifferentiated cells, anaemia and thrombocytopenia, and a slightly smaller percentage of blast cells in the myelogram (72%). However, the symptoms presented by both patients are characteristic of ALL in children.

The patient described in the literature was included in the Children's Oncology Group (COG) AALL1731 clinical trial, which included three drugs in induction treatment: vincristine, dexamethasone, PEG-asparaginase and intrameningeal chemotherapy. Treatment was complicated by seizures. At the end of induction, the residual disease was 2.18% blast cells. The patient underwent high-risk consolidation chemotherapy, and after four weeks of consolidation chemotherapy, the blast population increased to 3.6%. The patient received commercial chimeric CD19 antigen (CAR) T-cell therapy, achieving complete remission. Despite the treatment, a relapse occurred on the 177th day after CAR-T cell administration [9]. In the present patient, the response to induction treatment was good, and therefore protocol M was used, followed by protocol II according to AIEOP-BFM ALL 2017 for the IR group.

The comparison of the present patient with the only available description of a patient with analogous ALL highlights the importance of case presentation, showing how patients with RSTS respond to therapy in terms of disease response and side effect profile. The situation of the patients, seemingly very similar, from the first symptoms of acute leukaemia to the response to treatment and the range of side effects of therapy, was completely different.

CONCLUSIONS

Rubinstein-Taybi syndrome is one of the rare genetic diseases with an increased risk of benign and malignant tumours. This is one of the few cases of ALL in a patient with Rubinstein-Taybi syndrome. Therefore, there is a need for further research to find factors other than RSTS that would help determine the most appropriate therapeutic treatment.

Article information and declarations

Ethics statement: All persons who have contributed significantly to the work are listed as co-authors, and the work of others is cited accordingly. The work has not been submitted for review and publication in another journal.

Author contributions: Conceptualization: J.B. and M.L; methodology: I.K.; formal analysis: J.Z. and I.K.; resources: M.L.; data curation, I.K.; writing — original draft preparation: J.B. and I.K.; writing — review & editing: M.L. and J.Z..; visualization: I.K.; supervision: J.Z.

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REFERENCES

1. Michail J, Matsoukas J, Theodorou S. [Arched, clubbed thumb in strong abduction-extension & other concomitant symptoms]. Rev Chir Orthop Reparatrice Appar Mot. 1957; 43(2): 142–146, indexed in Pubmed: 13466652.
2. Van Gils J, Magdinier F, Fergelot P, et al. Rubinstein-Taybi syndrome: a model of epigenetic disorder. Genes (Basel). 2021; 12(7), doi: 10.3390/genes12070968, indexed in Pubmed: 34202860.
3. Spena S, Gervasini C, Milani D. Ultra-rare syndromes: the example of Rubinstein-Taybi syndrome. J Pediatr Genet. 2015; 4(3): 177–186, doi: 10.1055/s-0035-1564571, indexed in Pubmed: 27617129.
4. Korzus E. Rubinstein-Taybi syndrome and epigenetic alterations. Adv Exp Med Biol. 2017; 978: 39–62, doi: 10.1007/978-3-319-53889-1_3, indexed in Pubmed: 28523540.
5. Lee YR, Lin YC, Chang YH, et al. Genetic diagnosis of Rubinstein-Taybi syndrome with multiplex ligation-dependent probe amplification (MLPA) and whole-exome sequencing (WES): case series with a novel variant. Front Genet. 2022; 13: 848879, doi: 10.3389/fgene.2022.848879, indexed in Pubmed: 35464843.
6. Bentivegna A, Milani D, Gervasini C, et al. Rubinstein-Taybi syndrome: spectrum of CREBBP mutations in Italian patients. BMC Med Genet. 2006; 7: 77, doi: 10.1186/1471-2350-7-77, indexed in Pubmed: 17052327.
7. Boot MV, van Belzen MJ, Overbeek LI, et al. Benign and malignant tumors in Rubinstein-Taybi syndrome. Am J Med Genet A. 2018; 176(3): 597–608, doi: 10.1002/ajmg.a.38603, indexed in Pubmed: 29359884.
8. Mar N, Digiuseppe JA, Dailey ME. Rubinstein-Taybi syndrome — a window into follicular lymphoma biology. Leuk Lymphoma. 2016; 57(12): 2908–2910, doi: 10.3109/10428194.2016.1165816, indexed in Pubmed: 27086936.
9. Kurtz KJ, Tallis E, Marcogliese AN, et al. Near-haploid B-cell acute lymphoblastic leukemia in a patient with Rubinstein-Taybi syndrome. Pediatr Hematol Oncol. 2022; 39(8): 747–754, doi: 10.1080/08880018.2022.2049938, indexed in Pubmed: 35275800.
10. Saettini F, Herriot R, Prada E, et al. Prevalence of immunological defects in a cohort of 97 Rubinstein-Taybi syndrome patients. J Clin Immunol. 2020; 40(6): 851–860, doi: 10.1007/s10875-020-00808-4, indexed in Pubmed: 32594341.
11. Choi N, Kim HY, Lim BC, et al. Genetic and clinical heterogeneity in Korean patients with Rubinstein-Taybi syndrome. Mol Genet Genomic Med. 2021; 9(10): e1791, doi: 10.1002/mgg3.1791, indexed in Pubmed: 34427995.