Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 12 (61) No. 2 – 2019
https://doi.org/10.31926/but.ms.2019.61.12.2.3

POLYMORPH LYMPHOPROLIFERATION B AND COMMON VARIABLE IMMUNODEFICIENCY 2 *TACI MUTATION* IN A 13 YEARS BOY – CASE REPORT

D. VODĂ[1,2] L. DRACEA[1,2] M. BUCUR[1*]

Abstract: *Common variable immunodeficiency (CVID) is one of the most frequent types of primary immunodeficiency that manifest a great variability in symptoms and severity. We present a case of a 13 years old boy initially diagnosed with primary cellular immune deficiency (persistent lymphopenia) at the age of 3 years with repeated infections (staphylococcal infections, , herpes keratitis, onychomycosis, respiratory and digestive infections), afterward establishing the diagnosis of B polymorphic lymphoproliferation and common variable immunodeficiency 2 - TACI mutation, which for he is transferred to a clinic in Rome, Italy, in order to establish therapeutic conduct.*

Key words: *CVID, TACI mutation, lymphoproliferation, immunoglobulins*

1. Introduction

Common variable immunodeficiency (CVID) is one of the most frequent types of primary immunodeficiency that presents a great variability in symptoms and severity. It is a syndrome that impairs immune system, characterized by a reduced serum level of the classes of immunoglobulins G and immunoglobulins A, but also in IgM in about half of the cases. The diagnosis is based on the suggestive clinical symptoms for primary immunodeficiency, but also biological analyzes that include immunological and genetic tests. The etiology of this disease is unknown, the genetic cause is identified in about 10% of cases.

Common variable immunodeficiency (CVID) was associated with mutations in at least 13 genes, but the most frequent mutation occur in TNFRSF13B gene (encoding TACI -Transmembrane Activator and CAML Interactor). This gene produces a protein that is implicated in the maturation and survival of B cells, but also in antibodies production.

[1] Clinical Emergency Children's Hospital of Brasov,.
[2] Faculty of Medicine, *Transilvania* University of Braşov.
*Correspondent author: mihacri7@yahoo.com

The disease has two peaks of incidence between 2 and 5 years and between 16 and 20 years. The child affected by this pathology may have recurrent infections, mainly bacterial and viral infections in the respiratory tract (pneumonia, bronchitis, sinusitis), but also gastrointestinal, eyes, ears, skin. [2], [3], [4], [5], [6], [11].

The criteria reviewed in 2014 by the European society of immune deficiencies (ESID) registry for CVID diagnosis include at least one of the following: increasing susceptibility to infections, autoimmune disorders, granulomatous disease, unexplained monoclonal lymphoproliferation, family history of antibody deficiency and marked decrease of IgG and IgA, with or without decreasing IgM (at least two determinations below 2 standard deviations) compared to normal for age and at least one of the following: poor immune response to vaccinations, decreased memory B cell (less than 70% of normal value for age) and the exclusion of secondary causes of hypogammaglobulinemia and the establishment of the diagnosis after 4 years of age (but the symptoms may be present earlier) and the absence of a marked T lymphocyte deficit. [1]

2. Case presentation

We describe a case of a 13-year-old child initially diagnosed with cellular immune deficiency, who progressively revealed over time the diagnostic criteria for variable immunodeficiency variable 2 with TACI mutation and B-polymorphic lymphoproliferation due to Epstein Baar virus. He is the second child of the family, born naturally at the gestational age of 42 weeks, having a birth weight of 3900g, length 54 cm, presented with physiological jaundice, was vaccinated according to the national program and performed the prophylaxis of rickets until 1 year and 6 months. Hereditary history is insignificant. Medical history: at the age of 3 years he was diagnosed with primary cellular immune deficiency (persistent lymphopenia), with recurrent dermatitis and recurrent infections (staphylococcal infections, herpes keratitis, onychomycosis, respiratory and digestive infections) for which he required hospitalization and antibiotic, antifungal, and antiviral treatment.

In 2014, at the age of 10 years, he was admitted in our pediatric unit for digestive pathology. At that time, the patient was diagnosed with recurrent dermatitis and immune cell deficiency. The patient's blood tests showed lymphopenia, and immunoglobulin level detected low values for IgA and IgG.

In 2015 he returned to our hospital for cervical adenopathy, that was afterward remitted after antibiotic and anti-inflammatory treatment. The blood tests revealed minimal inflammatory syndrome and maintenance of lymphopenia. The patient received a referral for a specialized consultation in a clinic in the country specialized for the diagnosis of immune deficiencies for children, where he did not present.

In 2016, he returned for respiratory symptoms for which he was admitted 3 times during the year, the main symptom being persistent and irritating cough, but also the appearance of splenomegaly and hepatomegaly, with generalized lymph nodes. Blood tests revealed lymphopenia, low levels of IgA and IgG, inflammatory syndrome. Serologies were performed for Herpes simplex virus, Toxoplasma, Cytomegalic virus, Epstein Barr virus (EBV)

with increased IgG . Serologies for HIV and hepatitis viruses were negative. Under antibiotic, antiviral, corticosteroid and symptomatic treatment the evolution was favorable, with partial remission of adenopathy. Imaging investigations performed in February 2016 (chest CT) revealed a 15/13/11 mm nodular lesion in the lower lobe of the left lung and other small 5-6 mm adjacent nodular lesions, with bronchoalveolar infiltrates. QuantiFERON test was dosed with a negative result, and the pulmonologist has established the diagnosis of Chronic Interstitial Pneumonia, with the recommendation of evaluation in a specialized pneumology clinic, where he has not been presented. In December 2016, due to the recurrence of the generalized lymph nodes and the persistence of the cough, it is decided to perform a computed tomography for the cervical region, thorax, abdomen and pelvis that revealed: multiple cervical, abdominal lymph nodes, hepatomegaly, splenomegaly, medial inferior lobe tissue mass in the lower lobe of the left lung, tumor mass right upper renal pole (see table 1). The CT result brought into discussion the first intention a lymphoma. Therefore, bone marrow biopsy was performed within normal limits. Cervical lymph node biopsy was performed with immunohistochemistry, the result revealed histopathological aspect compatible with a polymorphic lymphoproliferation determined by Epstein Baar virus in the context of immunodepression (table 2). EBV DNA was dosed, much increased values (11889 IU/ml).

In February 2017, the basic profile lymphocyte immunophenotyping was performed, which revealed T, B lymphocyte deficiency and low CD4 / CD8 ratio, and the diagnosis of combined primary immunodeficiency was established, and we decided to initiate the immunoglobulin substitute treatment. The patient presented repeated hospitalizations for reassessment, but also for symptoms such as persistent productive cough, weight loss, loss of appetite. Chest CT examination revealed an increase in size of the formation of the left lung and pulmonary Aspergillosis was discussed in the immunocompromised patient. Antifungal treatment with Voriconazole iv and then orally, was initiated (anti-Aspergillus IgG antibodies - 12813U ml, NV <8.0). Further laboratory features revealed persistent lymphopenia, low Ig G and Ig A, elevated LDH, inflammatory syndrome present, DNA herpes virus type 1 and 2 negatives. At the end of October 2017 he presented on the left hand a round skin lesion with erythematous contour, center with necrotic aspect, appeared affirmatively after local trauma, with progressive growth in dimensions up to 5 cm with extension to the police, and proliferative and cauliflower appearance, with minimal continuity solution, which is why plastic surgery and biopsy sampling at the lesion level was performed. The histopathological aspect and the immunophenotypic profile excluded a proliferation of lymphoid nature, leaving a cutaneous granuloma under discussion – observing cutaneous Aspergillosis. Evolution shows the total healing of the skin lesion. (Figure 1).

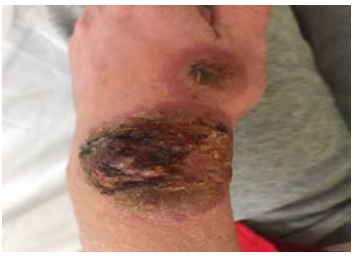

Fig. 1. *Cutaneous granuloma*

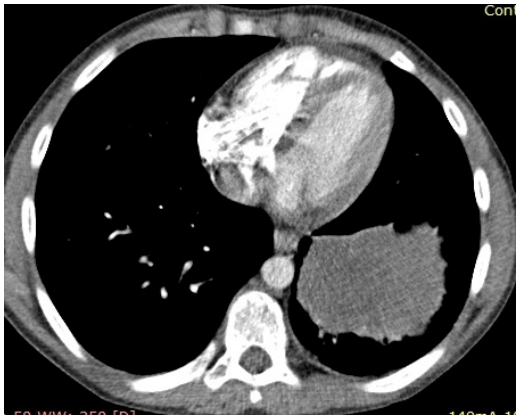

Fig. 2. *CT chest and abdomen October 2017*

In 2018 the patient had a prolonged hospitalization from January to April. On admission to our clinic in January 2018, he presented a productive cough and a tumor formation on the left axilla (axillar lymph node), with progressive growth, for which he received antibiotic treatment. Subsequent evolution was unfavorable, with persistent symptomatology, which is why chest CT was repeated, which showed an increase in size of the formation of the lower lobe of the left lung, compared to October 2017 (Figures 2 and 3).

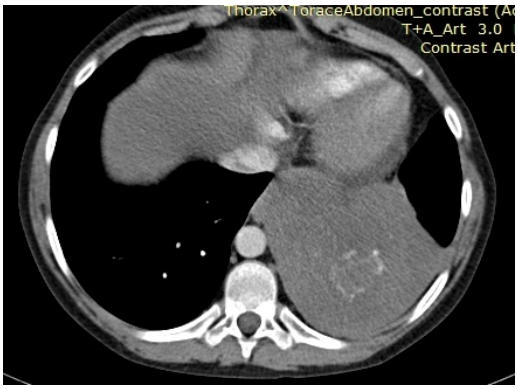

Fig. 3. *CT chest and abdomen February 2018*

Lymphoproliferative syndrome and non-Hodgkin's lymphoma with pulmonary lymphoproliferation, along with lymph nodes and renal lymphoproliferation in primary immune deficiency were discussed again. Lymphocyte immunophenotyping was repeated which revealed lymphopenia, low CD 4 / CD8 ratio, decreased B 19 lymphocytes, slight decrease in T lymphocytes. Genetic analysis detected a variant in heterozygous status in the TNFRSF13B gene also called Transmembrane Activator and CAML Interactor - TACI, located on chromosome 17p11.2. The phenotype described for mutations in the TNFRSF13B gene is associated with Variable Common Immunodeficiency 2 (CVID 2). Analysis of Ig G subclasses showed decreased Ig G2 and Ig G3, and response to vaccinations revealed poor response to tetanus vaccination. (table 2)

Based on typical symptomatology and clinical evolution, as well as laboratory data, including genetic testing, and respecting ESID criteria 2014, we finally included the case of variable common immunodeficiency 2 with TACI mutation and lymphoproliferative syndrome / non-Hodgkin's lymphoma. In April 2018, due

to the complexity of the case and the depletion of the therapeutic possibilities in Romania, we transferred the child in Italy, to the Bambino Gesu Scientific Recovery and Treatment Clinic in Rome.

Table 1

Imaging examinations (CT) in evolution

Date of examination	CT examination result with contrast substance
December 2016	Median basal tissue mass LIS, tumor mass right upper renal pole. Cervical-thoracic-abdominal-pelvic adenopathy, hepatomegaly, splenomegaly CT appearance brings into question the first intention a lymphoma
February 2017	Solid-liquid lesion LLS 7.5 / 7.5 / 6.5 cm, iodophile, Kidney lesion as upper pole 3.5 / 2.6 cm, not iodophilic (increase in size)
April 2017	Heterogeneous lesion solid-liquid LLS 7.73 / 6.2 / 4.52 cm, iodophilic
July 2017	LLS lung injury reduced in size 3.99 / 4.99 / 3.3 cm
October 2017	Mixed expansive process LLS 3.02 / 4.36 / 2.67 cm, iodophilic. Hyperdense kidney lesion as upper pole 0.85 cm
January 2018	Expansive process LLS 7.4 / 4.9 / 5.2 cm, iodophilic. Hyperdense nodular lesion 0.85 cm in right renal cortex upper pole

Table 2

Laboratory tests

Osteo-medullary aspiration 01.12.2016	Within normal limits
Ganglion biopsy with immunohistochemistry 01.11.2017	Histopathological appearance compatible with EBV polymorphic lymphoproliferation positive in the context of immunosuppression
Histopathological examination of skin biopsy 01.11.2017	Histopathological appearance and immunophenotypic profile exclude proliferation of natural hemato-lymphoid. Skin granuloma. In observation cutaneous Aspergillosis.
Immunophenotyping immune status 21.02.2018	**Lymphocytes=821** (VN: 1300-3000); B **lymphocytes =61** (200-500); **T lymphocytes=708** (1000-2000); **BL/CD19=6,9%** (VN: 8,6-25,6), **TL CD4+=120** (500-1300); TL **CD4+=6,7% (**33-66) TL CD8+=474(300-800); TL CD8+=92,3%(60-80); **rap. CD4/CD8=0,25** (1,1-1,4); **NK cells=51** (100-700)
Subclass IgG	IgG1=NV; **IgG2=0,62 g/l** (NV 1,10-4,85); **Ig G3=0,16** (NV 0,26-1,16)
Genetic analysis 15.05.2018	**TNFRSF13B**, variant with pathogenic significance, common variable immunodeficiency type 2
Immune response to vaccines	**Poor response to tetanus vaccination = 0,32 IE/ml** (NV over 10 IE/ml)

3. Discussions

Our case was initially diagnosed, at 3 years of age, with primary cellular immune deficiency based on major lymphopenia. Serum levels of IgA and IgG were inconsistent and insignificantly low. Until the age of 11, the clinical and serological characteristics remained unchanged, presenting with recurrent dermatitis, herpes keratitis, onychomycosis, staphylococcal skin infections, respiratory and digestive infections. At age 13, persistent respiratory symptomatology (tumor mass in left lung) and the onset of adenopathy, splenomegaly and hepatomegaly required further investigations (baseline lymphocyte immunophenotyping and lymph node biopsy with immunohistochemistry) that established first the diagnosis of combined humoral and cellular primary immunodeficiency (deficiency of lymphocytes B, lymphocytes T and NK), then, after specific genetic test, common variable immunodeficiency (CVID) and lymphoproliferative EBV polymorphism. It was difficult to set lymphoma diagnosis without lung biopsy for tumor mass, but in Italy was performed and nonHodgkin lymphoma with B large cell it was established and received chemotherapy: Rituximab, Ifosfamide, Carboplatin Etoposide (R-ICE protocol) and Ibrutinib, Nivolumab.

Epstein Barr virus infects about 95% of the population, but most people remain asymptomatic. Hyun-Jung Kim and colleagues, in a study published in 2017, discuss the involvement of the Epstein-Barr virus in multiple B-cell lymphoproliferative disorders associated with immune deficiency, Hodgkin's lymphoma and non Hodgkin lymphoma. Also, EBV T cell lymphoproliferative diseases have been associated with peripheral T cell lymphomas, T-cell angioimmunoblastic lymphomas, NK / T cell nasal extra nodal lymphomas, aggressive NK cell leukemia, and other rare histologic types [7], [8].

Due to the presence of lymphoproliferative syndrome and cutaneous granuloma, characteristic manifestations for variable common immunodeficiency were completed investigations with dosage of IgG subsets (low IgG2 and IgG3), poor response to antitetanic vaccination and genetic analysis that detected a variant in status TNFRSF13B gene.

Thus, the diagnosis of variable common immunodeficiency was established with certainty, 10 years after the first diagnosis of primary immune deficiency.

The TNFRSF13B gene also called Transmembrane Activator and CAML Interactor - TACI is located at chromosome level 17p11.2. Missense variant c.310T> C (p.Cys104Arg) shows coverage instead of 126X, has been reported in the literature and in other patients, predictive analyzes in silico classify it as 7/7 pathogen and it is classified as pathogenic variant according to The American College of Medical Genetics and Genomics (ACMG) guide. The phenotype described for mutations in the TNFRSF13B gene is associated with Type 2 Variable Common Immunodeficiency. In most cases of variable common immunodeficiency, no pathogenic mutation is identified.

However, in 7-10% of patients the patients present a mutation of the TACI-encoded TNFRSF13B gene, a member of the tumor necrosis factor receptor family expressed on B cells. TACI binds two

ligands, one that induces proliferation (APRIL) and one that induces B cell activation (BAFF), both recording increased values in patients with variable common immunodeficiency. In patients with a single TACI mutation associated with variable common immunodeficiency, development of an autoimmune disease is likely, while patients with two mutant alleles do not have clinical features of autoimmune disease, suggesting the complex role of the TACI gene in maintaining B cell tolerance. [10]

Consequently, variable common immunodeficiency with TACI mutation is associated with malignant or autoimmune diseases. Lymphoma is one of the more severe complications of CVID. This increased risk are unclear, although it seems to be multifactorial with the combination of genetics, immune dysregulation, and chronic infectious agents including oncogenic viruses such as Epstein–Barr virus. CVID-associated lymphomas are more likely to be of B cell origin with a predominance of non-Hodgkin lymphoma (NHL), and these usually occur in adult and are rarely seen in children. NHL is frequently extranodal, and although the parotid gland, sinuses, orbital cavity, and stomach can be affected, the majority of cases affects the lung . [9]

4. Conclusions

We presented a difficult case with delayed diagnosis of CVID initially associated with polyclonal lympho-proliferation related with EBV infection with evolution towards secondary malignancy- B large cell non-Hodgkin lymphoma.

An increased risk of malignancy particularly that of lymphoma and gastric cancer is associated with CVID. Patients with polyclonal lymphadenopathy were shown to have fivefold increased risk of lymphoid malignancy. Lymphoid malignancy generally occurs late in disease and in patients with pre-existing polyclonal lymphocytic infiltration. However, lymphoma can appear in young pediatric CVID patients in the absence of previous polyclonal lymphadenopathy.

References

1. Ameratunga, R., Brewerton, M., et al. *Comparison of diagnostic criteria for common variable immunodeficiency disorder, hypothesis and theory article*. In Front. Immunol., (2014), 15.
2. Bonilla, F., Geha, R.: *Common Variable Immunodeficiency.* In: Pediatr Res (2009), 65, 13–19.
3. Cerempei, L., Ghinda, S., et al.: *Imunodeficienţele primare la copii: etape de diagnostic*. In: Curierul medical, (2012), nr.3 (327).
4. Erdem, S.B., Gulez, N., et al.: *Characteristics of the patients followed with the diagnosis of common variable immuno-deficiency and the complications.* In: Cent Eur J Immunol. (2019); 44(2):119-126. Epub, Jul 30.
5. https://ghr.nlm.nih.gov/condition/common-variable-immune-deficiency
6. https://rarediseases.org/rare-diseases/common-variable-immune-deficiency/
7. Hyun-Jung, K., Young, H.K., et al.: *Hematopathology Study Group of the Korean Society of Pathologists. Epstein-Barr Virus–Associated Lympho-proliferative Disorders:*

Review and Update on 2016 WHO Classification. In: J Pathol Transl Med. 2017 Jul; 51(4): 352–358.

8. Leonardi, L., Lorenzetti, G., et al.: *Rare TACI Mutation in a 3-Year-Old Boy With CVID Phenotype.* In: Front. Pediatr., 15 October 2019.
9. Mortaz, E., Tabarsi, P., Adcock, I. et al.: *Cancer related to immunodeficiencies: Update and. Perspectives.* In: Frontiers in Immunology (2016 sept.), vol. 7 (365).
10. Romberg, N., Chamberlain, N., et al.: *CVID-associated TACI mutations affect autoreactive B cell selection and activation.* In: J. Clin Invest, (2013 Oct.), 123 (10).
11. Urschel, S., Kayikci, L., et al.: *Common Variable Immunodeficiency Disorders in Children: Delayed Diagnosis Despite Typical Clinical Presentation.* In: The Journal of Pediatrics, (June 2009), Vol. 154, Issue 6, p. 888-894.