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REVIEW ARTICLE

VIA MEDICA

Pulmonary alveolar proteinosis in the course of ICF type 2 syndrome

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Abstract

In this article, we would like to present rare diseases, which are immunodeficiency, centromeric instability and facial dysmorphism syndrome (ICF), and myelodysplastic neoplasm (MDS), with possible complications of their course and treatment with particular emphasis on pulmonary alveolar proteinosis (PAP). We are basing that review on our experience that we have gained through the diagnostic and treatment process of our pediatric patient. MDS is a rare disease among children that has a different and uncharacteristic clinical course and genetic background in comparison to MDS occurring in adults. Regarding the uncharacteristic clinical picture, the differential diagnosis can be a challenge for clinicians. In that process also diseases characterized by immunodeficiency should be taken into account, including the ICF. ICF type 2 is an autosomal recessive disease that manifests by agammaglobulinemia or hypogammaglobulinemia, developmental delay, and facial anomalies. Both ICF and MDS can be treated with an allogeneic hematopoietic stem cell transplantation. One of the possible complications in the course and treatment of MDS and ICF can be PAP. Its pathogenesis is based on the accumulation of surfactant in alveoli that leads to pulmonary insufficiency. As hematologic diseases and their treatment are known for their impact on multiple systems, we find the unique value of this article in being the first description of the coexistence of ICF type 2 with PAP.

Key words: myelodysplastic syndrome, immunodeficiency, centromeric instability and facial dysmorphism syndrome, pulmonary alveolar proteinosis, *ZBTB24* gene

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Introduction

Myelodysplastic neoplasm (MDS) is considered a heterogeneous group of malignant hematopoietic disorders [1–3]. It is also very rare disease among children accounting for less than 5% of pediatric hematologic malignancies [4]. It is not only rarer in that population in comparison to adults, but it also differs in chromosomal aberrations and clinical presentation [4].

Immunodeficiency, centromeric instability and facial dysmorphism syndrome (ICF) is an autosomal recessive disorder manifesting as agammaglobulinemia or

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hypogammaglobulinemia, developmental delay, and facial anomalies [5, 6]. We can divide ICF into four types depending on the mutations of particular genes [5, 7] There have been described slightly over 100 cases of ICF in total [5]. The ICF type 2 (ICF2) is caused by a homozygous or complex heterozygous mutation in the zinc finger and BTB domain containing 24 gene (*ZBTB24*) on chromosome 6q21, which leads to the loss of its function [8]. Reaching a precise diagnosis is possible based on next-generation sequencing (NGS), which identifies the specific mutation [8]. In the therapy of ICF, the essential treatment features immunoglobulins injections and hematopoietic stem cell transplantation [6, 7, 9].

Pulmonary alveolar proteinosis (PAP) is a rare interstitial pulmonary disease, which is caused by the excessive accumulation of surfactant in alveoli leading to respiratory insufficiency. Treatment relies on whole lung lavage (WLL) via a double-lumen endotracheal tube with the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy, rituximab, statins and hematopoietic stem cell transplantation (HSCT) or even lung transplant depending on the source of the disease [10–12].

This study aims to present these rare conditions that occurred in our patient which include myelodysplastic neoplasm, hematological complications, immunodeficiency, pulmonary alveolar proteinosis and mutation of the *ZBTB24* gene.

Material

Patient's medical history and examination findings have been obtained from Department of Pediatric Hematology and Oncology and Transplantology in Lublin and Department of Pediatric Pneumonology and Allergy in Warsaw.

The mother of the patient gave written informed consent to describe and publish her child's case.

Case

The child was born in the 38th week of gestation. Pregnancy was complicated with hydrothorax of the fetus. After childbirth the girl was intubated due to pneumonia. During that hospitalization the morphology check-ups have been showing megaloblastic anemia and leukoneutropenia, therefore the B12 vitamin supplementation was applied. The medical state of the child was normalized, however supervision of her morphologic parameters was maintained.

At age of 5 months laboratory test results confirmed significant lymphopenia, agranulocytosis and further presence of antigranulocyte antibodies and IgG4 levels increased. In the myelogram, there were increased levels of erythroblasts with the presence of hypoplastic lymphoreticulocytic system. Clinical data indicated the suspicion of severe combined immunodeficiency (SCID) or MDS.

During the next examinations at the age of 13 months, clinicians observed retardation of psychomotor development — inability to walk, stand and speak. In that time three episodes of thrombocytopenia occurred, which were treated successfully with steroids and immunoglobulins. Despite the therapy, episodes of thrombocytopenia recurred. Therefore, rituximab was applied, giving only temporary improvement. Meanwhile, the follow-up trepanobiopsies showed the presence of Howell-Jolly bodies, increased levels of erythroblasts and megakaryocytes along with the reduced function of lymphoreticulocytic system.

Increasing and persistent anemia and leukopenia with features of dysplasia in several trepanobiopsies were premises to perform allogeneic hematopoietic stem cell transplantation (allo-HSCT), which was accomplished successfully when the girl was 2,5 years old. Despite primary promising examinations of chimerism, further tests within the next years showed a decrease in presence of transplanted cells in bone marrow.

3 months after the procedure of allo-HSCT, the patient was admitted to the hospital with symptoms of pulmonary insufficiency. Computed tomography scans showed ground glass opacities and thickening of septal lines suggesting the diagnosis of pulmonary fibrosis. After treatment featuring azithromycin, steroids, salbutamol and oxygen therapy, temporary resolution of symptoms has been achieved. One month later the pulmonary symptoms exacerbated, so there was a necessity of introducing long-term corticosteroid therapy. The following attempts of steroids withdrawal resulted in recurrence of pulmonary symptoms, so it was decided to add azathioprine to the treatment and therefore to reduce dosage of steroids. Good response to steroid therapy combined with recently underwent allo-HSCT, suggested the diagnosis of idiopathic pneumonia syndrome.

However, results of bronchoscopy and histopathology examination of biopsy taken during treatment with full dose of steroids enabled the diagnosis of PAP with symptoms of lung fibrosis. Due to unsatisfactory effects of pharmacological treatment, the girl underwent WLL, that gave only a short-term remission of pulmonary symptoms. Because of constant saturation decreases the patient required full-time oxygen therapy. The next therapeutic option was to qualify the patient for the nintedanib treatment of proteinosis-related pulmonary fibrosis, however, the girl didn't meet the inclusion criteria.

When the patient was 6-year-old there was an NGS examination performed on oral mucosa fibroblasts using SureSelect Custom Constitutional Panel with the NextSeq 550 machine. Results showed verified heterozygous *ZBTB24* c.[1222T>G] cysteine-to-glycine missense mutation, which enabled the possible diagnosis of ICF2.

At the age of 7, the girl died of respiratory failure.

Literature review and discussion

MDS and allo-HSCT

According to the 5th edition of the World Health Organization (WHO5) classification of pediatric MDS, it can be divided into three main categories, which are based on the number of blasts in the bone marrow or in blood and the occurrence of *TP53* mutation [13]. These categories are MDS with low or increased blasts and MDS with bi-allelic *TP53* inactivation. The most important diagnostic criteria are persistent, unexplained cytopenia and morphologic dysplasia [3, 13]. Typical morphology of bone marrow in the course of MDS consists of hypocellularity and morphologic dysplasia [14]. There are significant differences that distinguish pediatric MDS and MDS that occurs in adults including a genetic background of the disease and atypical clinical course in children [15, 16]. Genetic aspect is connected with mutations in germ lines and oncogenes, which are rarely seen in adults' cases [17, 18]. Karyotype changes, such as chromosome 7 monosomy, are more frequently diagnosed in pediatric patients [16, 18]. Pediatric MDS can also be associated with chromosomal instability syndromes and disorders of epigenetic regulators, which set an important connection with genetic abnormalities found in our patient [13]. When it comes to the clinical distinction of pediatric MDS involves more frequently occurring symptoms of bicytopenia than isolated anemia [15]. The choice of allo-HSCT as a treatment for patients with myelodysplastic neoplasms is determined by patient and disease related factors. Despite the high risk, this procedure remains the only potentially curative method and decreases the risk of transformation into acute myeloid leukemia (AML). Our patient has showed symptoms of bone marrow insufficiency, mainly regarding myelopoiesis since early childhood. Pancytopenia, dysplastic features in the bone marrow and the clinical state of the child were premises to diagnose MDS and indicated performing allo-HSCT [15, 19]. In our patient's case the myeloablative procedure before allo-HSCT consisted of fludarabine, treosulfan, and thiotepa. Such a combination of cytostatics has a low rate of relapse incidence and was proven effective in patients with pediatric MDS [20]. As allo-HSCT is known as an effective therapy for various diseases, it is also connected with many complications and side effects [21]. In the post-transplantation period, we can mainly observe symptoms of acute and chronic graft-versus-host disease (GvHD) and the occurrence of secondary malignancies [21]. Another possible complication of allo-HSCT can be PAP [22].

Immunodeficiency, centromeric instability and facial dysmorphism syndrome type 2

However, there were clinical features, that couldn't have been entirely explained by MDS, which involved a delay in psychomotor development, facial dysmorphic features and immunological abnormalities — especially a low level of lymphocytes. Such clinical presentation could have been related to a mutation of the *ZBTB24* gene, which was diagnosed briefly before the child's death. Genes, participating in DNA methylation are known as crucial factors in the pathogenesis of MDS and ICF [5, 7, 23]. Mutations in genes, such as: *TET2*, *DNMT3A*, and *IDH1/IDH2* are identified in more than a half of the MDS cases. Their role is creating a methylation pattern of DNA, rather than maintaining it. Also effect of loss of their function is observed in diseases affecting mainly myeloid stem cells [24]. ICF can be divided into four types depending on the mutations of particular genes: *DNMT3B* (ICF1), *ZBTB24* (ICF2), *CDCA7* (ICF3), and *HELLS* (ICF4) [5]. Some authors also mention ICF X with unknown gene dysfunction [7]. When it comes to *ZBTB24*, it plays an important role in the maintenance of the methylation pattern of DNA. Furthermore, this gene is a transcription regulator with a particularly high expression in juvenile type B lymphocytes and it is crucial during the process of the immunoglobulin class switching [8, 25]. *ZBTB24* gene mutation prompts suspicion towards ICF2, which is an autosomal recessive disorder. Despite that, there are descriptions of patients with ICF symptoms, who were compound heterozygous for the *ZBTB24* gene with serine-to-stop nonsense mutation [c.833C>G, p.Ser278X] and a cysteine-to-glycine missense mutation [c.1222T>G, p.Cys408Gly] [8]. In this case only heterozygous *ZBTB24* [c.1222T>G, p.Cys408Gly] cysteine-to-glycine missense mutation has been verified. However, basing on characteristic symptoms and the fact that dysfunction of the *ZBTB24* protein can be determined by various mutations, which may still be unknown, we assume that girl may have had an ICF2 syndrome. The ICF syndrome is mostly diagnosed at a young age, following recurrent gastrointestinal and respiratory tract infections, sepsis and a failure to thrive [5, 26]. The immunodeficiency in ICF patients may manifest in low or undetectable amounts of IgA, IgG and IgM to an agammaglobulinemia or reduced T and B cells levels [6]. The girl, like most of the reported cases, had immunodeficiency encompassing lowered immunoglobulins and T- and B-cells levels. However, due to an early substitution of immunoglobulins, we haven't noticed an increased number of infections. We have noticed thrive issues including delayed growth and speech development. Delayed growth has been observed even before allo-HSCT was performed, but the aggressiveness of this therapy may have had its impact [27]. Other symptoms may include facial anomalies such as hypertelorism, epicanthic folds, micrognathia, low-set ears, and macroglossia. Mentioned characteristics are variable and usually mild. Moreover, the ICF manifestations may include intrauterine growth retardation, protruding abdomen, thin arms and legs, bipartite nipples, scleral telangiectasias, skin pigment changes like café au lait spots or irregularly outlined mildly hyperpigmented spots [5, 6].

In the case of our patient, we can indicate short stature, genu valgum, protruding abdomen, thin upper and lower limbs. The remaining appearance changes of the girl are related to the long-term corticosteroid therapy including weight gain, rounding of the face and an increase in adipose tissue around the base of the neck. Yet another group of symptoms is mental retardation and neurologic defects, which include slow cognitive and motor development and psychomotor impairment [5, 6, 26]. Even though our patient also struggled with mental and psychomotor development, the intensity of those manifestations was low. Abnormal cerebral development may be another ICF feature, as in one reported case authors suggest that mutation of *ZBTB24* gene might be connected with the occurrence of cerebral arachnoid cyst [28].

Mortality rate of the ICF2 is estimated on the level of 20% with opportunistic and pulmonary infections as the main cause of death [6, 29, 30]. Most of them die at a young age, usually in the first or second decade of life [29, 31]. Prognosis among ICF patients are usually better in cases without combined-type immunodeficiency, while gastrointestinal problems leading to diarrhea and thrive issues significantly worsen them [6, 29]. Therapeutical options in ICF2 include immunoglobulin replacement therapy and allo-HSCT. Immunoglobulin replacement therapy restricts frequency of recurrent respiratory infectious diseases [30, 32]. Another option, that was considered in other clinical cases, is an allo-HSCT [29, 30, 33]. There are only a few reports of performed allo-HSCT in patients with ICF type 1, who were successfully cured, and even fewer that presented the same outcome in patient with ICF type 2 [9, 29, 34–36]. Positive results presented in those papers give premises to take allo-HSCT under consideration in patients, whose clinical state allows performing that procedure.

Pulmonary alveolar proteinosis

In this clinical report, not only hematological problems were the cause of the patient's condition, but it has also been determined by pulmonary symptoms, which occurred after allo-HSCT. PAP is a very rare pediatric syndrome. Direct cause of symptoms is an excessive accumulation of surfactant in alveoli that leads to respiratory insufficiency. As a result, patients report cough and progressive dyspnea, less frequently fatigue, weight loss, and chest pain [10, 11, 37]. Physical examination often does not reveal any pathological symptoms, rarely crackles may be heard during auscultation and/or digital clubbing may be observed [10, 11, 38]. It mainly presents as an autoimmune PAP, which almost only occurs in adults [37]. It is estimated that the prevalence of all pediatric PAP may be lower than one in 1,000,000 [38]. PAP can be divided into 3 forms: congenital, primary (autoimmune) and secondary. Congenital PAP is caused by mutations in encoding the GM-CSF receptor or surfactant proteins. Primary, the most common form in adults, stands out with higher levels of anti-GM-CSF antibodies showing its autoimmune character [37]. Secondary PAP is associated with hematologic disorders (like myelodysplasia, myeloid leukemia, lymphoma, plasma cell disorders), non-hematologic malignancies, lysinuric protein intolerance, sideroblastic anemia, dermatomyositis, congenital or acquired immunodeficiency, immunologic diseases and within immunosuppression. Other possible causes are the usage of some drugs, exposure to certain dust and infections [11, 37, 39–41]. The direct mechanism of surfactant accumulation may result from its disrupted recycling featuring alveolar macrophages or type II pneumocytes which are caused by non-functional T and B lymphocytes [40]. There are many reports about PAP coexisting with immune deficiency, including severe combined immunodeficiency, common variable immunodeficiency and infection with the human immunodeficiency virus [38, 42, 43]. In the case of our patient, alveolar proteinosis may have resulted from diverse sources like immunodeficiency (agammaglobulinemia or immunosuppression connected with HSCT), hematologic disorder resembling MDS, infections, or even drugs, which were used during therapy [11, 37]. Patients suffering from PAP have increased risk of infections, with that rate even higher in patients with secondary PAP [12]. Moreover, infections are one of the most important factors that can lead to death, what also applies to our patient [12].

Treatment of PAP is based on WLL which is used as a symptomatic treatment when pulmonary symptoms exacerbate, patient requires oxygen treatment or when diffusion lung capacity for carbon monoxide (DLCO) declines [12, 44]. WLL was also a part of our patient's treatment, but it gave only brief mitigation of symptoms. Other possible paths of therapy depend on the source of disease and include usage of GM-CSF therapy, rituximab, statins and HSCT or even lung transplant [10–12].

Conclusion

The case of our patient, on which we based that review, is unique mostly due to the concomitance of several very rare diseases involving different systems. Pediatric hematologic syndromes can adopt misleading and vague clinical courses. Thus, it is vital to use all diagnostic methods, including NGS, to establish the diagnosis. The precise identification of the disease with emphasis on specific mutation and patient's comorbidities may affect the selection and success of treatment, especially in high-risk procedures such as allo-HSCT. For this reason, it seems that wide-range differential diagnosis with establishing all diagnoses is so important. Moreover, it is worth remembering that hematologic diseases and their treatment can affect many systems of the human body. Thus, we should be vigilant in terms of possible side effects and complications.

Article information and declarations

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Author's contributions

MC, TB — conceptualization. MC, KD, TB, KK — validation. PH, WH, UJ — investigation. PH, WH, UJ, MC, TB — resources. PH, WH — data curation. PH, WH, UJ — writing: original draft preparation. MC, TB, KD, KK, PH, WH, UJ — writing: review & editing. MC, TB, KD, KK — supervision. MC — project administration. All authors have approved the final article.

Conflict of interest

Authors declare no conflict of interest.

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Supplementary

There are no supplementary materials.

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