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CASE REPORT

CDC42 mutation related to systemic inflammatory response with severe repercussions in a 17 years old patient: a case report

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Abstract

The CDC42 gene is a member of the family of small Rho GTPases, which performs a wide spectrum of physiological functions in regulating the cell cycle (adhesion, polarity, proliferation, migration, motility and activation of cell transcription). Its mutation can result in a heterogeneous group of phenotype and manifestations. If the mutation occurs in the C-terminal portion (determined by exome genetic examination), together with clinical criteria (pancytopenia, auto-inflammation, skin rash and episodes of hemophagocytic lymphohistiocytosis), NOCARH syndrome will be characterized. Treatment can be carried out with corticosteroids, immunosuppressants, immunomodulators or monoclonal antibodies, with the definitive treatment being hematopoietic stem cell transplantation. This case report aims to add knowledge about NOCARH syndrome, which is complex syndrome and still little known in the literature, helping with earlier diagnosis as well as adequate and timely intervention.

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INTRODUCTION

CDC42, a product of the CDC42 gene - cell division cycle 42 - is a member of the small Rho family GTPases , which play a broad spectrum of physiological roles in cell cycle regulation, including adhesion, polarity, proliferation, migration, motility, and activation of cellular transcription [1,2]. CDC42 mutation results in a heterogeneous group of phenotypes and manifestations, since different *missense mutations* have already been identified throughout the coding sequence of this gene using whole exome sequencing[3,4]. The genotype-phenotype relationship may be better clarified as more patients are identified[5].

The main clinical features of this mutation include growth alterations, facial dysmorphism, intellectual disability, cardiac defects, immunological, hematological and lymphatic abnormalities and brain malformations[1,3]. Within the spectrum of manifestations, there is the description of a new hematological and autoinflammatory phenotype caused by a *de novo* mutation in the CDC42 gene in its C-terminal portion, the NOCARH syndrome (*Neonatal onset of pancytopenia , autoinflammation, rash and episodes of hemophagocytic lymphohistiocytosis*), characterized by neonatal onset of pancytopenia, autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis[1,5]. To date, approximately 15 cases of this syndrome have been described in the literature[6].

Exome sequencing is used to identify the CDC42 gene mutation[3]. Treatment varies according to the clinical manifestations presented by patients, depending on the location of the mutation. Because it is considered autoinflammatory , acute episodes of NOCARH syndrome, as in the case reported, can be managed with different classes of medications, such as corticosteroids, immunosuppressants, immunomodulators, and monoclonal antibodies. Definitive treatment consists of hematopoietic stem cell transplantation (HSCT)[7].

In this case report, we present a 17-year-old patient with a CDC42 gene mutation associated with a severe systemic inflammatory response. She was diagnosed with NOCARH syndrome and treated with an immunomodulatory medication. Informed consent was obtained from both the patient and her legal guardian, authorizing publication.

CASE REPORT

A 17-year-old female patient presented with a history of acute nasopharyngitis 15 days prior to admission, which progressed to fever, inflammatory signs in the left cervical region (pain, edema, hyperemia, and local heat), and vomiting for 2 days. She also reported a 6 kg weight loss in 2 months.

Admitted, she received treatment with ceftriaxone and clindamycin. A chest and cervical CT scan identified left anterior cervical edema and reactive lymph nodes, with no signs of abscess or collection. She developed septic shock, respiratory failure, and required intensive care unit support . She was intubated, and vasoactive drugs such as vasopressin, norepinephrine, milrinone , intravenous corticosteroids, and vitamin C were initiated. A chest X-ray was consistent with ARF (Figure 1). The antibiotic regimen was modified to piperacillin-tazobactam, linezolid, and fluconazole, with the antimicrobials continued for 10 days.

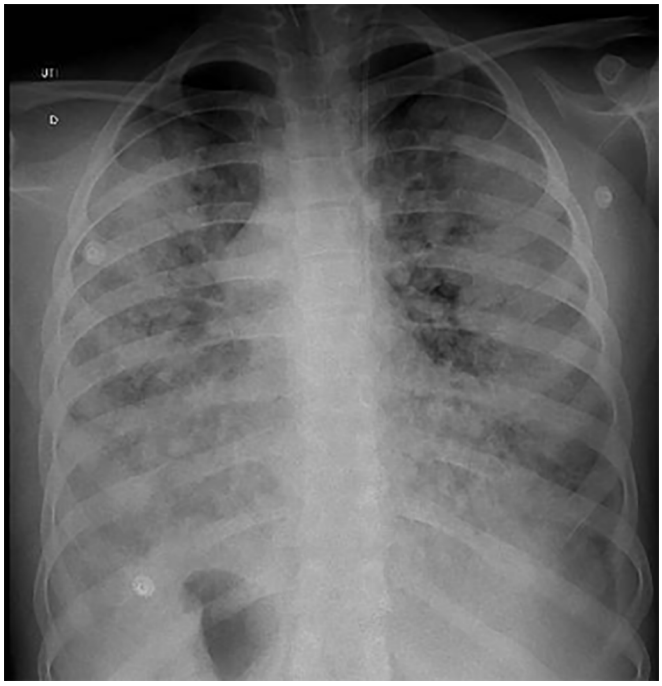

Figure 1. Chest radiograph compatible with ARDS.

The patient had an uneventful history of pathology during the neonatal period. She developed chronic leukopenia and thrombocytopenia at age 6, and was followed up jointly with a hematologist. She was initially investigated for myelodysplasia, neoplasia, and rheumatologic diseases, with negative results. As described in Tables 1 to 4, we have the initial diagnostic investigation tests (complete blood count showing chronic bicytopenia; immunophenotyping for the sublymphocyte population; bone marrow aspirate; and immunoglobulin levels, with emphasis on IgM immunoglobulin, with a value above the reference value for her age). She was diagnosed with the CDC42 mutation through exome scanning in September 2019 (at age 13), as shown in exome Figure 2. She had two previous hospitalizations (streptococcal pharyngotonsillitis / nasopharyngitis with thrombocytopenia). No family history of immunodeficiency, grandmother diagnosed with Systemic Lupus Erythematosus.

After discussion with the immunology and rheumatology teams, a diagnostic hypothesis of NOCARH syndrome was raised. Laboratory tests revealed pancytopenia and elevated lactic dehydrogenase levels, along with other findings suggestive of hemophagocytic syndrome, clinically fulfilling the diagnostic criteria.

Table 1. Hemograms showing chronic bicytopenia.

	September 23, 2013	12/09/2014	Reference values
Hemoglobin	12.3	12.4	11.5 – 15.5 g/ dL
Hematocrit	40%	36.2%	33 to 46%
Leukometry	1960	2370	4 – 10 thousand
Differential	Neutrophils 50% (980) Sticks 3% (58,8) Eosinophils 5% (98) Lymphocytes 38% (744,8)	Neutrophils 64% (1516.8) Sticks 5% (118.5) Eosinophils 2% (47.4) Lymphocytes 23% (545.1)	1800 - 7000 /uL 0 - 1100 /uL 0 - 600 /uL 1200 - 5000 /uL
Platelets	122 thousand	70 thousand	150,000 to 450,000 /µL

Table 2. Immunoglobulin dosage (RV: reference values).

	Dates	
	12/14/2018	**02/06/2022**
IgA	83 (VR 52-468)	111 (VR 47- 249)
IgE	15 (VR 2 - 696)	13 (VR 2- 629)
IgG	950 (VR 640 - 1700)	1173 (VR 640- 1700)
IgM	267 (VR 50 - 250)	325 (VR 50 – 300)

Table 3. Bone Marrow Aspirates Bone.

	September 30, 2013	January 14, 2019	January 19, 2024
Cellularity, leuko-erythroblastic ratio	60%; 3.7:1	Slightly decreased cellularity in the extension and normal cellularity in the spicules; 2.1:1.0	Intensely hypocellular, Erythroid Ratio : 9.8:1.0.
Red and granulocytic series	Normal	Granulopoiesis 61.0% of cells, with cells in all stages of maturation, without signs of dysplasia.	Erythropoiesis 6.0% of cells (decreased, predominantly orthochromatic) Granulomonopoiesis : 59.0% of cells (normocellular), predominance of segmented neutrophils
Lymphocytes	Normal	11% of the cells, some of which are hematogones	35% of cells
Megakaryocytes and plateletgenesis	Gifts and Normal	Present, without platelets around (platelets are in decreased quantity throughout)	Absent

Tofacitinib was indicated , with significant improvement after administration of the medication. Currently undergoing monthly outpatient follow-up with the pediatric rheumatology team, and until the 3-month post-hospital discharge consultation, there were no new complications and no adverse effects of the medication.

DISCUSSION

The diagnosis and delineation of new genetic syndromes are difficult, given the limited availability of patients, genetic heterogeneity, and clinical variability[1]. Recent studies provide new information that expands the spectrum of human diseases associated with CDC42 mutations. CDC42, an intracellular member of the Rho family of GTPases, is a key regulator of cell polarity. By regulating the assembly of actin cytoskeletal structures spatiotemporally, CDC42, in partnership with RAC and RHO A, controls cell shape and movement. Thus, CDC42 plays an important role in migration and directed functions, processes that are essential for embryonic development, hematopoiesis, immune system function, growth, and cell proliferation[4].

As a GTPase, CDC42 functions as an intracellular molecular switch. It alternates between two forms—an active form when bound to GTP, and an inactive form when bound to GDP. When activated, CDC42 undergoes a conformational change that allows it to associate with membranes and interact with effector molecules, which in turn undergo their own conformational changes to exert downstream biochemical functions[4].

Beginning in 2015, the first patients with a de novo heterozygous *missense mutation in CDC42 at* p.Tyr 64Cys were reported, associated with a constellation of features termed Takenouchi-Kosaki syndrome , which includes dysmorphism,

Table 4. Immunophenotyping for lymphocyte subpopulation (04/12/2022).

CELLULARITY:			
Number of Leukocytes:	3870	cells/uL	
* The percentage corresponds to the total cellularity.			
Lymphocytes: 13.30%;	**Neutrophils:** 81.30%;	**Monocytes:** 1.70%	
Eosinophils: 2.90%;	**Basophils:** 0.80%;	**Dendritic Cells:** 0.00%	

RESULT	**RELATIVE** (%)	**ABSOLUTE** (cells/uL)	**Reference Values, Profile** (cells/uL) (10-16 years)
Total Lymphocytes:	13.3	514.71	**1,000-5,300**
FROM THE LYMPHOCYTE WINDOW:			
T lymphocytes (CD3+):	76.4	393.24	**800-3,500**
CD3+CD4+:	28.6	147.21	**400-2,100**
CD3+CD8+:	40.9	210.52	**200-1,200**
CD3+CD4+CD8+:	0.2	1.03	**There is no**
CD3+CD4-CD8+:	6.7	34.49	**There is no**
CD4/CD8 ratio:	11.7	---	**0.98-3.2**
B lymphocytes (CD19+):	13.7	70.52	**200-600**
NK lymphocytes (CD3-/CD16+/CD56+):	9.9	50.96	**70-1,200**

RESULT

The following variant was identified

Gene	Position (GRCh37)	Variant (HGVS)	Population Frequency	Zygosity	Classification
CDC42	chr1: 220405072	NM_0017931.3:c.101C>A (p.Pro34Gln)	-	Heterozygosity	VUS

VUS – Variant of uncertain meaning.

Figure 2. Exome collected on 09/02/2019.

developmental delay, macrothrombocytopenia, and, in one case, immunodeficiency[8,9]. In 2018, Martinelli and colleagues reported 15 additional patients with de novo heterozygous *missense mutations* in CDC42, several of which were recurrent[10]. Disease features shared by the patients included poor growth, facial dysmorphism, neurodevelopmental abnormalities, and cardiac malformations, in addition to hematologic and immunologic aberrations[10].

More recently, the wider use of whole- exome sequencing in patients with complex conditions has led to the discovery that heterogeneous disease phenotypes may be associated with mutations in the same gene. Lam et al.[1] reported patients with recurrent de novo heterozygous *missense mutations in CDC42 at* p.Arg 186Cys, a variant not previously associated with Takenouchi-Kosaki syndrome. These patients had a different disease, termed NOCARH, characterized by neonatal onset of pancytopenia, autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis (HLH)[1].

HLH has been characterized as a clinical syndrome with hyperinflammation driven by the excessive activation and expansion of macrophages and CD8+ T lymphocytes. Typical features include persistent high fever, splenomegaly, liver involvement, coagulation disorders associated with pancytopenia, and, usually, increased ferritin. The mechanisms underlying this disease are diverse. Mutations leading to defective cytotoxicity by natural killer (NK) and CD8+ T lymphocytes are the typical cause of monogenic HLH, typically termed primary HLH. However, a significantly higher number of patients present with HLH in the absence of genetically defective cytotoxicity in the context of infections, inflammatory rheumatic diseases, and malignancy[1].

We report on a 17-year-old patient with a previously known CDC42 gene mutation who, related to acute pharyngitis, developed a systemic inflammatory response with severe repercussions, meeting clinical criteria for NOCARH syndrome. She was treated with tofacitinib, with a good therapeutic response. Tofacitinib , a drug from a new therapeutic class (a selective inhibitor of JAK1, JAK2, and JAK3), acts within cells by inhibiting the activity of JAK kinase enzymes, which prevents the production of inflammatory cytokines, resulting in a decreased inflammatory response. Tofacitinib is a JAK-selective immunosuppressant widely used in rheumatoid arthritis and psoriatic arthritis. It reduces lymphocyte proliferation and activation and has infrequent serious adverse effects, the most

common being serious infections (an adverse effect present with immunosuppressive medications in general). Other reported adverse effects include hyperlipidemia and diarrhea, making it important to monitor lipid profiles, blood counts, and liver function tests quarterly. A limiting factor for its use is its high cost, but in the case reported, a donation was obtained in a timely manner for treatment. High-dose hydrocortisone was also administered due to refractory shock. Prior to tofacitinib treatment, immunoglobulin treatment was attempted, but it was not tolerated. After the first immunoglobulin infusion, the patient developed TRALI (transfusion-associated acute lung injury), and the immunoglobulin treatment plan was suspended.

Cytokine levels[7]. Among the inflammatory cytokines involved, interleukin 18 (IL-18) has been a biomarker for the diagnosis of NOCARH and syndromes related to dysregulation of CDC42 function. The likely role of IL-18 would be to stimulate IFN-γ production. This helps explain why most patients described in the literature show improvement after treatment with IL-1 and/or IFN-γ antagonists[1]. Furthermore, pharmacological inhibition of the JAK1/2 signaling pathway is a known potent treatment option for several IFN-induced autoinflammatory conditions, acting on fibroblasts, and can lead to clinical control of autoinflammation[6]. This latter mechanism of action was successfully used as a therapeutic option in the reported case.

CONCLUSION

This document presents a case report of a female patient with a history of chronic bicytopenia and suspected immunodeficiency. The CDC42 mutation was already known through exome analysis , but the pathogenicity of this variant had not yet been confirmed when the test was performed. Upon admission, the patient developed a severe condition and met diagnostic criteria for NOCARH syndrome, and specific treatment was instituted.

As more patients are identified, it becomes possible to better elucidate genotype-phenotype relationships. Therefore, more detailed studies of other variants are needed to elucidate the genesis of immunological/ autoinflammatory disease and why some patients with the same variants may not manifest in the same way. Clearly, there is much more to be studied about how the CDC42 gene functions physiologically in humans and how its mutation presents clinically.

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