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REPORT

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Hemophagocytic syndrome in a patient with Fanconi anemia and VACTERL association

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ABSTRACT

Introduction: Hemophagocytic syndrome results from hyperactivity of histiocytes and lymphocytes, triggered by infections, mainly viral by cytomegalovirus, Epstein-Barr and herpes. Fanconi anemia (FA) is a rare genetic disease with heterogeneous symptoms common to other diseases such as VACTERL, a disease of unknown etiology in which there are several congenital malformations. The concomitance of Fanconi and VACTERL anemia occurs in 5 to 30% of FA patients. **Report:** A 14-month-old male infant was admitted to investigate fever, hepatosplenomegaly, and granulopenia. The patient was diagnosed with hemophagocytic syndrome due to hyperferritinemia, bone marrow hemophagocytosis, transaminase elevation, decreased fibrinogen, and cytomegalovirus (CMV) infection confirmed by serology and PCR. The test with mitomycin C (MMC) showed chromosomal fragility. The patient was diagnosed with a VACTERL/FA association for having a clinic and a test compatible with both FA and VACTERL. **Conclusion:** The VACTERL/FA association is seldom described, but is present in pediatric medical practice. This study presented the main clinical-laboratory aspects and reviewed the main aspects of the concurrence of this pathology.

Keywords: lymphohistiocytosis; hemophagocytic; Fanconi anemia; congenital abnormalities; cytogenetics; chromosome fragility.

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INTRODUCTION

Hemophagocytic syndrome (HS) is a rare but potentially fatal disease that arises from the hyperactivity of histiocytes and lymphocytes. It can be present primarily or secondarily. The primary form is due to mutations in autosomal recessive genes that encode proteins related to the process of cytotoxic granule exocytosis during programmed natural killer (NK) cell death. Acquired secondary hemophagocytic syndrome (SHS) can arise from various conditions such as immunodeficiencies, rheumatologic diseases, malignancies, and infections. The most frequent infection is the virus of the herpes family, but bacterial, fungal, and parasitic pathogens can also trigger the disease[1,2].

Fanconi anemia (FA) is a rare disease with a heterogeneous clinical and genetic profile. The main signs and symptoms described in the disease arise from congenital bone abnormalities and bone marrow failure that may lead to a picture of aplastic anemia.

These patients have a high risk of mortality from malignancies such as myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[3,4]. The etiopathogenesis of the disease results from mutations in genes involved in DNA repair and mostly presents an autosomal recessive profile, but an X-linked profile can be observed when the *FANCB* gene is affected, or more rarely an autosomal dominant profile when the *FANCR* gene is affected[5,6].

VACTERL associations are congenital malformations resulting from structural abnormalities of the embryonic mesoderm, whose etiology is unknown and each letter corresponds to a clinical abnormality. The diagnosis is made by the simultaneous occurrence of at least three of the following congenital malformations: vertebrae (absent vertebrae, hemivertebrae, butterfly vertebrae, vertebral fissures, and fusions), ribs (absent ribs, supernumerary ribs, fusions, and division), limbs, heart, kidneys, anorectal and tracheoesophageal fistula[7,8].

This study describes a patient diagnosed with SHS by cytomegalovirus (CMV) who presented with congenital skeletal abnormalities of the vertebrae, thumb hypoplasia, unilateral renal agenesis, absence of microcephaly, and Fanconi face, characteristic of the disease. The chromosomal fragility test with mitomycin C (MMC) showed positivity, characterizing the diagnosis of Fanconi anemia associated with VACTERL.

REPORT

A 14-month-old male infant from Recife, Brazil was taken to the pediatric emergency room due to a cough associated with daily fever and hypoxia for 7 days; in the last 24 hours, he had three emetic episodes. On admission, the patient was afebrile, cyanotic, tachycardic, and tachydyspneic (respiratory rate 42 breaths per minute, saturation 96%). On respiratory auscultation, he had diffuse rales and expiratory wheezing. Laboratory tests showed: Hemoglobin: 11.7 g/dL; Hematocrit: 28.7%; White cell count: 26.8x10^{3}µL (Segmented 82%; Eosinophils 0%; Basophils 0%; Lymphocytes 14%; Atypical lymphocytes 0%; Monocytes 3%); Platelets: 450x10^{3}µL. Abdominal ultrasound revealed the absence of the left kidney and hepatosplenomegaly. Chest X-ray showed perihilar condensation on the right, the presence of a hemivertebra (D12), and scoliosis on the right. The patient was treated with cefepime but persisted with daily fever, there was diffuse exanthema and palpable lymph nodes in cervical and inguinal chains. CMV serology revealed positive IgM and quantitative polymerase chain reaction (PCR) for CMV detected 4,960 viral copies. Other viral serologies and cultures for fungi and bacteria were negative. Laboratory tests showed ferritin 17.759ng/mL, transaminases (AST 185U/L and ALT 110U/L), LDH 913UI/L and fibrinogen 494mg/dL. The patient was diagnosed with cytomegalovirus (CMV) associated SHS and treated with ganciclovir and intravenous dexamethasone. Due to the associated bone deformities, he was transferred to the Pediatric Oncology Center for follow-up and investigation of chromosomal fragility syndrome which was confirmed by testing with MMC (Table 1 and Figure 1a), the conventional bone marrow cytogenetic study showed normal karyotype (46,XY) (Figure 1b). The patient was diagnosed with SHS secondary to CMV and FA. During outpatient follow-up, it was observed that the patient did not have a face typical of FA, had renal agenesis, a renal alteration rarely described in FA, and other skeletal abnormalities, such as hemivertebrae, were not consistent with FA, thus the hypothesis of VACTERL association was considered, following the necessary criteria shown in Table 2. The patient is being followed up as an outpatient with granulopenia and remains stable, with no need for therapy. However, the human leukocyte antigen (HLA) system of the patient and genitors was requested, as well as the registration in the REREME.

This study was submitted to the Research Ethics Committee with CAAE approval number 73905817.1.1001.5192.

DISCUSSION

Patients with FA have a high risk of infectious processes that is due to abnormalities of adhesion, migration, phagocytosis, recruitment, and mobilization of inflammatory monocytes[9] especially if associated with granulopenia, caused by bone marrow failure. This case reports a patient with a CMV infectious process associated with HS confirmed through clinical and laboratory data who was successfully treated with ganciclovir and dexametasona. Due to the abnormality of the right thumb (Figure 1c), the patient was also investigated for chromosomal fragility testing by MMC and confirmed as FA. However, the patient did not have the café-au-lait spots and Fanconi face that is characteristic of the disease; instead, he had mild to moderate macrocephaly (Figure 1d), hemivertebrae (Figure 1e), and scoliosis, both on the right, and renal agenesis, unusual findings in patients with FA.

FA is a rare autosomal recessive disease with heterogeneous manifestations. This diversity makes diagnosis difficult, due to the many differential diagnoses. The main features of FA are skeletal abnormalities (Table 1) that may occur in other frailty syndromes, such as Rothmund-Thompson syndrome and its variants[10], but also other pathologies such as VACTERL or VACTERL-H association, a disease estimated in 1/40,000 live births[11].

The patient described in this paper evolved with granulopenia, and so far no pancytopenia, which is characteristic of the disease in a later stage (7-8 years), has appeared. This could be due to hemophagocytosis, but as it appeared months after the SHS, it made

Table 1: Result of chromosomal fragility test by MMC.

Culture	General Events	Analyzed events/cells	Anormal events/cells	Anormal cells (%)
Without MMC	4	0.08	1.3	6%
With MMC	48	0.96	1.3	66%

us assume that the granulopenia is a consequence of medullary hypoplasia due to the chromosomal instability syndrome and not the SHS. Besides presenting other symptoms of FA, such as thumb hypoplasia and chromosomal fragility test with a high number of breaks, and how, the patient had no microcephaly, typical triangular facies, and no skin pigmentation changes, frequent findings in FA. On the other hand, the patient had renal agenesis and other skeletal abnormalities such as hemivertebrae and marked scoliosis on the right and frequent changes in VACTERL association. The patient was diagnosed with VACTERL/FA association, which is described in 5% of these cases. Rothmund-Thompson syndrome and variants were ruled out since the patient had no skin alterations and had chromosomal fragility, findings not found in this pathology[10].

Evidence for the link between FA and VACTERL was first demonstrated by Porteous et al.[12], by analyzing two unrelated male patients who had features of both diseases and had chromosomal breaks in the MMC test. In agreement with the finding of Porteous, Giampietro et al.[13] demonstrated a high correlation between the presence of the VACTERL association and FA, by restudying 376 patients with FA, in which 37 (10%) presented at least three manifestations of VACTERL. After this finding, chromosomal fragility testing should always be performed in both VACTERL-H and VACTERL patients who present with radial and thumb changes, skin changes, growth retardation, microcephaly, and microphthalmia[14].

Table 2: Clinical manifestations described in concomitant FA and VACTERL.

Symptoms	%	Patient
VACTERL		
Vertebral anomalies/ribs (Hemivertebrae)	**60-95% (80%)**	**Present**
Anal atresia	55-90%	Absent
Tracheoesophageal Fistula	50-80%	Absent
Cardiac alterations	40-80%	Absent
Renal alterations (Renal Agenesis)	**50-80% (61%)**	**Present**
Limb skeletal abnormality	**40-50%**	**Present**
Fanconi anemia		
Thumb abnormality	**35%**	**Present**
Vertebral Anomalies	**2%**	**Present**
Flappy Ears	10%	Absent
Cardiac Alterations	6%	Absent
Renal alterations (Renal Agenesis)	**20% (5%)**	**Present**
Café au lait stains	40%	Absent
Hematological alterations	**90%**	**Present**

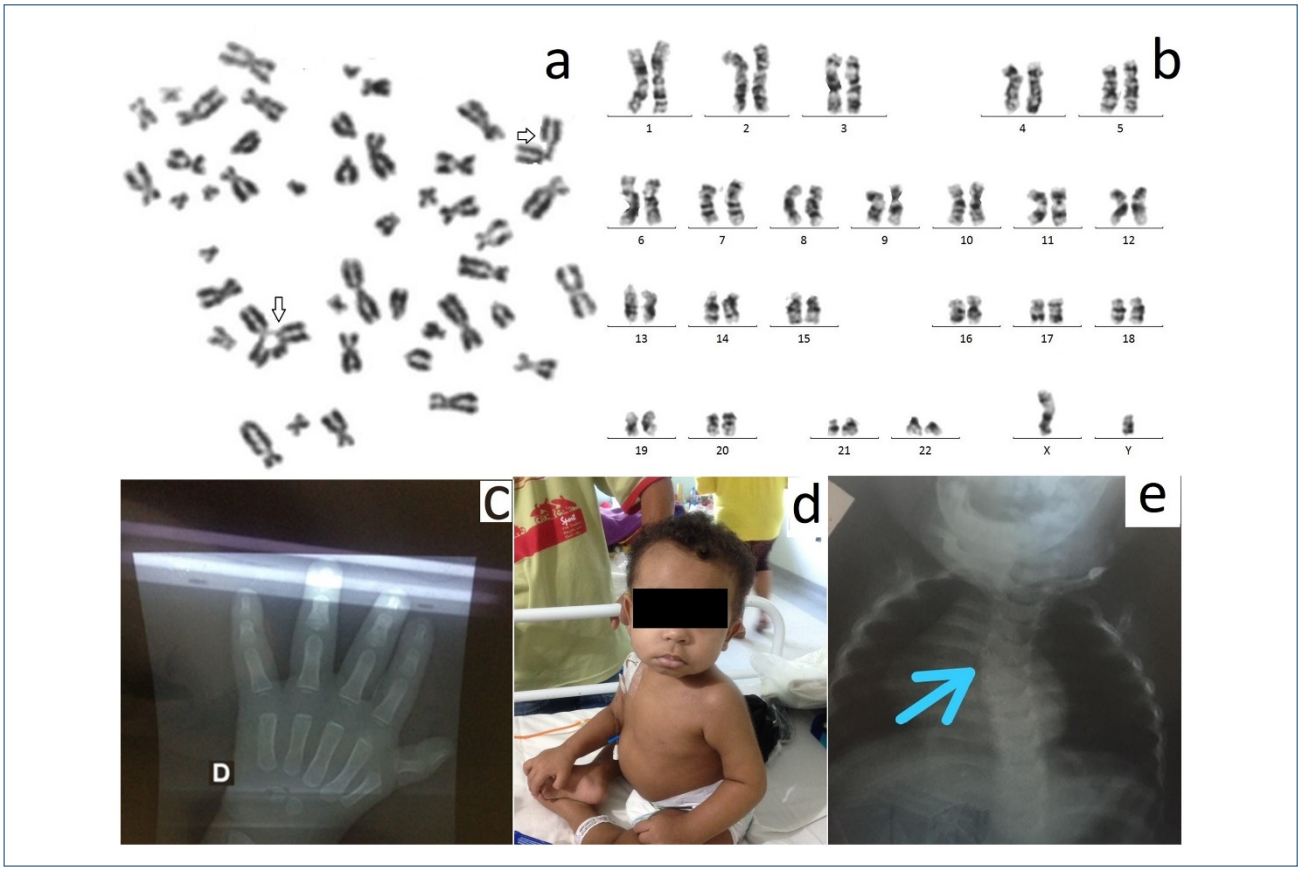

Figure 1: A) MMC test showing chromosomal variants (radial figures and chromosome breakage being pointed out) B) Bone marrow karyotype without abnormalities (46, XY) C) Clinical features of the patient: Macrocephaly and absence of Fanconi's face. D) X-ray of the right hand showing thumb hypoplasia. E) X-ray showing hemivertebra (D12).

Similar to the case described in this report, Botto et al.[15] found that carriers of FA and VACTERL-H have a higher frequency of limb abnormalities (preferably in the radius and/or thumb) and vertebral abnormalities (e.g., scoliosis), and a few cases had anal atresia, and none with FA had a tracheoesophageal fistula. While, Alter e Rosenberg[7] studied 2245 patients with FA and found that 118 had FA and VACTERL association, 90% of these patients had renal defects and skeletal alterations of the limbs (mainly radius and fingers).

Thus, the patient in this report was diagnosed with FA/VACTERL association and is stable in outpatient follow-up. At the moment, he is suffering from mild granulopenia (1,400 granulocytes). Patients with FA/VACTERL have greater involvement of the *FANCD1* gene, as well as shorter survival and a higher and earlier incidence of cancer compared to FA patients[7].

Since at least 5% of patients with FA can be classified as having the VACTERL association, it is up to the geneticist to observe these patients in childhood to consider the diagnosis of FA, through the chromosomal fragility test, consider genetic counseling for the family and refer them to the pediatric hematologist for follow-up. In this way, it will be possible to know the real incidence of this association.

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