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CASE REPORT

Fanconi's anemia in a pediatric patient

Anemia de Fanconi em paciente pediátrico

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ABSTRACT

Fanconi Anemia (FA) is a rare genetic autosomal-recessive disorder characterized by progressive spinal depression, morphological alterations such as café-au-lait spots, absence of fingers, genital atrophy, hypogonadism, short stature, susceptibility to myelodysplastic events, among others. We report a 10-year-old patient who sought medical care for evaluation of phimosis and bilateral retractile testis. There was an absence of the first right finger, café-au-lait spots, and syndromic facies, in addition to thrombocytopenia and abdominal pain. The chromosomal fragility test confirmed the clinical suspicion of FA. The investigation is complex and clinical evidence is essential for confirmation. The most appropriate treatment is bone marrow transplantation, which may lead to resolving hematological symptoms, as was the case in question.

PALAVRAS-CHAVE
Anemia de Fanconi
Fimose
Manchas café com leite
Relato de caso
Transplante de medula óssea

RESUMO

A Anemia de Fanconi (AF) é um distúrbio genético raro, herdado de maneira autossômica recessiva, e caracterizado por uma depressão medular progressiva, alterações morfológicas, como manchas café-com-leite, ausência de quirodáctilo, atrofia de genitália, hipogonadismo, baixa estatura, susceptibilidade a eventos mielodisplásicos, dentre outros. Trata-se de um paciente de 10 anos que procurou atendimento médico para avaliação de fimose e testículo retrátil bilateral. Verificou-se ausência do primeiro quirodáctilo direito, manchas café-com-leite e de fácies sindrômica, além de plaquetopenia e dores abdominais. O teste de fragilidade cromossômica confirmou a suspeita clínica de AF. A investigação é complexa e a clínica essencial para confirmação. O tratamento mais adequado é o transplante de medula óssea, podendo acarretar a cura dos sintomas hematológicos, como foi o caso em questão.

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INTRODUCTION

Fanconi Anemia (FA) is an autosomal recessive disorder triggered by chromosomal instability characterized by progressive spinal cord insufficiency, congenital abnormalities, and a strong predisposition to developing myelodysplasia, leukemia, and solid head/neck tumors. Hematological manifestations appear around the age of eight. Mutations that occur in the genes of patients with FA prevent DNA repair from being done correctly, and this activates cell apoptosis, leading to depletion of hematopoietic stem cells, causing pancytopenia[1]. The presence of malformations in the skin (café-au-lait spots), skeletal system (alterations in the thumbs and radius), central nervous system, genitourinary tract, and others are well-reported[2].

The diagnosis of FA is based on clinical manifestations and medical history and thus confirmed by spontaneous cytogenetic changes induced by clastogenic agents. Supportive care includes transfusion of blood products and management of infectious complications. The adequate treatment for long-term control is bone marrow transplantation, which can cure hematological symptoms, as in the case of the patient described[1]. This report was submitted and approved by the Research Ethics Committee of UNIFENAS (CAAE 47209421.1.0000.5143, decision nr. 4.807.321). All standards for conducting human studies established in Resolution CNS 466/12 were respected, and the person responsible signed the informed consent form.

CASE REPORT

RHT, ten years old in 2021, male, arrived in 2012 for evaluation due to phimosis and bilateral retractile testis.During the physical examination, the absence of the first right finger, café-au-lait spots in the right hypochondrium and lumbar region (Figures 1 to 3), in addition to the presence of syndromic facies, were noted. His mother reported mild hearing loss. Thrombocytopenia and anemia were evidenced (red cells 4.2 million/mm^3; hemoglobin 11.9 g/dL; hematocrit 39%; MCV 81 fL; MCH 28.1 pg; MCHC 32.4 g/dL; platelets 97,000/mm^3; leukocytes 11,600/mm^3).

Because of the hematological alterations, bone deformities, and characteristic patches on the skin, the possibility of the diagnosis of FA was highlighted, which was confirmed by the chromosomal fragility test, which detected a high number of chromosomal breaks, confirming the diagnosis, so the patient was referred for treatment.

In 2015, an allogeneic bone marrow transplant was performed from the mother's cells, preceded by chemotherapy for seven days to prepare the patient's marrow. Three days after transplantation, graft-versus-host rejection was diagnosed, and prednisone 15 mg was administered daily for two years. He attended an annual follow-up at a specialized hospital and semiannual follow-up at a hematology clinic.

In 2017, he returned reporting recurrent urinary infections, and in the same year, postectomy was performed, and orchidopexy (correction of the retractile testicle) and right inguinal herniorrhaphy were performed the following year.After postectomy, there was the resolution of recurrent urinary infections. Also, in 2017, a liver alteration was found (AST 43 U/L and ALT 75 U/L), with ursodeoxycholic acid being prescribed 150 mg orally daily. In 2018, he returned

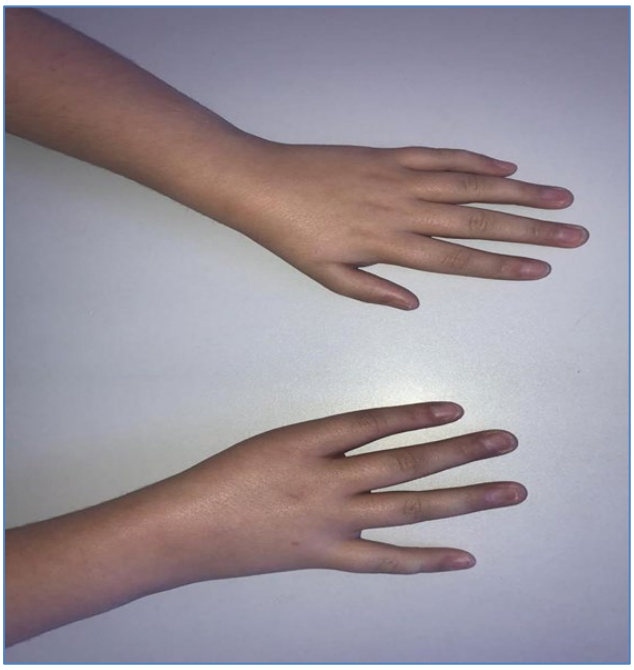

Figure 1 — Absence of the first right finger.

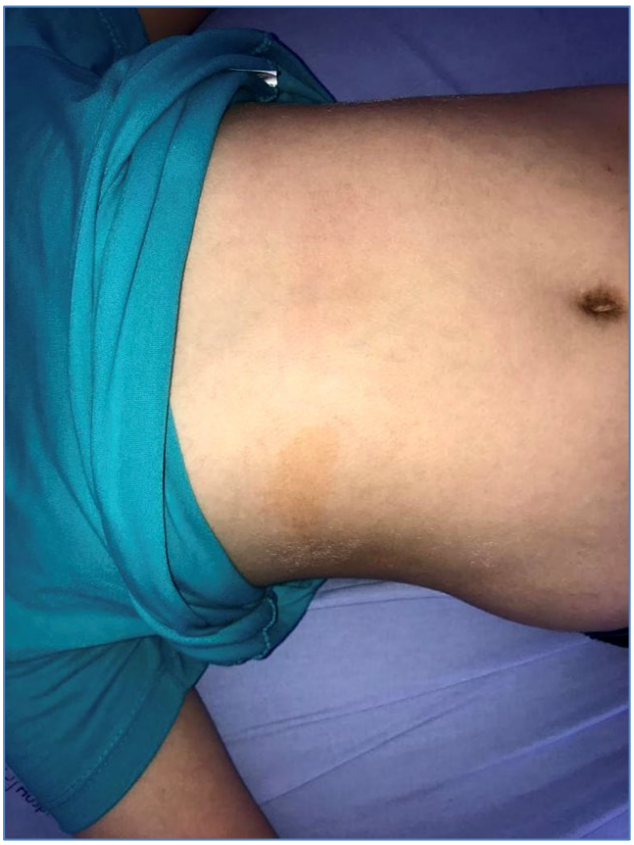

Figure 2 — Café-au-lait spots.

with laboratory tests suggestive of hypothyroidism (TSH 6.0 UI/mL and free T4 0.4 ng/dL), and levothyroxine 12.5 mg daily was prescribed. Nowadays, the patient is well, leading a life without limitations and complications.

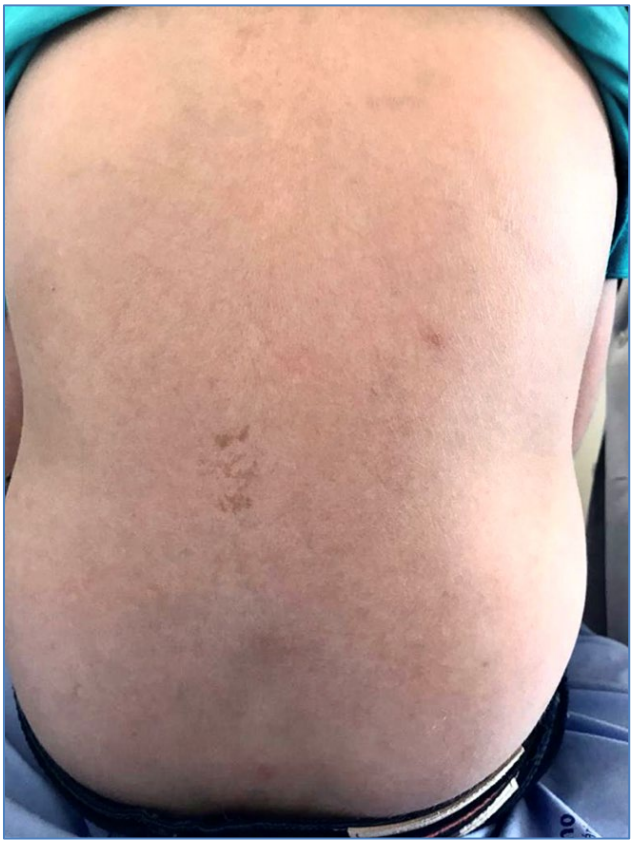

Figure 3 — Café-au-lait spots.

DISCUSSION

Fanconi Anemia is a heterogeneous recessive disorder, described by bone marrow aplasia, with a prevalence of 0.5 to 2.5 per million newborns, with a frequency of occurrence of 1:300[3,4]. It is characterized by physical abnormalities, bone marrow failure, and an increased risk of malignancy. Physical abnormalities are present in approximately 75% of affected individuals and include one or more of the following: short stature, abnormal skin pigmentation, skeletal malformations of the upper and/or lower limbs, microcephaly, and ophthalmic and genitourinary tract abnormalities[5].

The frequency of abnormalities in the development of the genital tract is higher in patients with FA than the rest of the population[6,7]. Among the male genital problems are micropenis, cryptorchidism, hypospadias, phimosis, azoospermia, and small testes for age and pubertal condition[6,7]. The reported patient had phimosis and bilaterally retractable testicles, and postectomy and right orchidopexy surgery was performed to resolve the conditions.

It is common to find hematological abnormalities in patients with FA, with the median age of presentation being seven years (ranging from birth to 31 years)[1]. When they are born, hematological values are usually normal. However, especially in the first decade of life, signs of hematological abnormalities appear[2]. The reported patient had thrombocytopenia, being diagnosed in consultation at the hematology clinic.

In this case report, the mother described mild hearing loss. Patients with FA may have hearing loss or anomalies[8]. Otological manifestations include morphological anomalies that affect ear structures, and hearing loss is usually conductive, but sensorineural hearing loss was also observed[6].

Another clinical finding in FA is hypothyroidism. About 60% of individuals have primary hypothyroidism, which, despite its mechanism being uncertain, is generally not autoimmune in nature[7].

Due to the late onset of anemia compared to other cytopenias, differential diagnoses, and the high variability in phenotype, a correct clinical diagnosis is complex and can be prolonged. This fact can be very harmful to patients[9].

The primary method to confirm the diagnosis of FA is the chromosomal degradation test, which is based on the cellular hypersensitivity of affected persons to DNA-chain cross-linking agents such as mitomycin C and diepoxybutane. To proceed with this test, a sample of the patient's peripheral blood is used. An analysis is performed by counting the number of chromosomes and specifically observing each one so that any failure, breakage, or rearrangement caused by the chemical agent can be visualized[10]. The test is highly sensitive and specific yet inaccessible on most factors due to its sophistication. Fortunately, the patient in question was well assisted, being tested, and had quick access to treatment.

Allogeneic hematopoietic cell transplantation was performed, which is the only curative therapy for hematological manifestations[5]. This treatment can restore hematopoiesis in the long term. However, some patients may present with disease-specific complications, such as endocrinopathies and increased risk of squamous cell carcinoma[12]. Allogeneic transplantation is determined as the precursor cells of the marrow originating from another individual, according to the level of compatibility of the blood material. Here, the patient's mother showed compatibility; in this way, she was the donor.

Before the abovementioned procedure, the patient underwent chemotherapy for seven days. The recipient who will receive the donor's cells should undergo a conditioning regimen; thus, the patient will be induced to immunosuppression through high-dose chemotherapy or radiotherapy to eradicate the initial disease, leaving room for the transplantation of the new marrow[13]. This approach minimizes host toxicity and causes less graft-versus-host disease[14]. Notably, despite the patient in question has undergone chemotherapy, he developed the disease. Graft-versus-host disease is a clinical syndrome characterized by fever, nausea, vomiting, diarrhea, and liver disorder. It is commonly observed in allogeneic bone marrow transplants, which can be acute or chronic, affecting approximately 50% to 80% of transplant patients[15].With the quick and accurate diagnosis of FA, it was possible

to establish an adequate approach and treatment with a satisfactory outcome.

CONCLUSION

Currently, the diagnosis and treatment of FA are complex. Diagnosis is achieved by clinical history and physical examination. Confirmatory testing is done through spontaneous and diepoxybutane-induced reactions. A timely, correct, and urgent diagnosis is needed due to the early evolution of the disease and the need to find compatible donors for future hematopoietic stem cell transplantation.

Bone marrow transplantation remains the best therapeutic option and the only possible cure for hematopoietic symptoms. Given the wide variation in the clinical presentation, the small number of cases reported in the literature, and the high morbidity of different forms of treatment, the description of cases such as this one is fundamental.

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Critical revision of the article: ASDS, AKPJ, CLC
Final approval of the manuscript*: AKPJ, CLC, FLF, GFLC, RDVS, ASDS
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