CASE STUDY

Fanconi anemia with neutropenic colitis: An unusual case report

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Abstract

Fanconi anemia (FA) is a rare, genetically inherited autosomal recessive disorder that manifests as bone marrow failure syndrome. Defects in genes with 16 complementation groups alter the stability of the DNA which is characterized by congenital malformations and progressive pancytopenia. This, in turn, can predispose to acute myeloid leukemia and other solid tumors. The most common diagnostic methods used in the detection of FA includes bone marrow biopsy and chromosome breakage test. We report a case of a 6-year-old Asian female child who presented with major complaints of lower abdominal pain, difficulty in swallowing, generalized tiredness, and gum bleeding. Her physical features were manifested as short stature, partial ptosis, hypopigmented spots on both hands, and thumb hypoplasia. Her bone marrow aspiration and biopsy showed markedly hypocellular bone marrow with reduced trilineage hematopoiesis which was suggestive of FA.

Key words: Autosomal recessive, bone marrow biopsy, chromosome breakage test, Fanconi anemia, hypocellular bone marrow, pancytopenia

INTRODUCTION

Fanconi anemia (FA) is a rare, genetically inherited autosomal recessive disorder and was first described in the year 1927 by a Swiss Paediatrician Guido Fanconi. It manifests as bone marrow failure syndrome and is characterized by congenital malformations and progressive pancytopenia. It can predispose to acute myeloid leukemia and other malignancies such as myelodysplastic syndrome and squamous cell carcinomas of the head and neck.[1,2] The various genes that are responsible for FA include FANCA, FANCB, FANCC, BRCA2 (FANCD1), FANCD2, FANCE, FANCF, FANCG (XRCC9), FANCI, BRIP1 (FANCJ or BACH1), FANCL, FANCM, PALB2 (FANCN), RAD51C (FANCO), SLX4 (FANCP), and *FANCQ*.[3] Among these, mutations in *FANCA* account for about 60–65% of the FA cases.[4] The incidence of FA is approximately 1–5/million, one out of every 136,000 newborns are affected with this disease. It is universally seen in children between 5 and 15 years of age.[2,5] Physical abnormalities seen in FA patients include café-au-lait spots (hyperpigmented patches), malformed thumbs or forearms, short stature, heart defects, gastrointestinal abnormalities, abnormalities of the eyes (small or abnormally shaped eyes) and the ears (malformed ears and hearing loss), abnormalities of the brain and the spinal cord such as hydrocephalus and microcephaly, malformations of the reproductive system, and the genital tracts (infertility), renal anomalies like malformed or absent kidneys, and other defects of the urinary tract.[6] The most common diagnostic methods used in the detection of FA includes bone marrow biopsy and chromosome breakage test. Among these methods, chromosome breakage test is considered as the reliable cellular marker for FA.[7] Diverse management methods used in treating FA include supportive therapy, androgen therapy, and curative therapy. Blood transfusion (packed RBCs [PRBCs] and platelets) is considered as the best supportive therapy for FA. Patients with severe neutropenia respond better to granulocyte-colony-stimulating factor. Androgens such as oxymetholone, danazol, and oxandrolone act by

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stimulating the proliferation of hematopoietic stem cells in FA patients. However, allogenic hematopoietic stem cell transplantation (HSCT) is the only proven long-term curative therapy for FA.[2]

CASE PRESENTATION

A 6-year, 10-month-old Asian female child was admitted in the pediatric department with major complaints of lower abdominal pain, difficulty in swallowing, and gum bleeding. On admission, the child had generalized tiredness and was prone to easy fatiguability. Her physical examination revealed that the patient had consistent weight with short stature (Ht: 120 cm; Wt: 18.5 kg) [Figure 1], partial ptosis [Figure 2], hypopigmented spots on both hands, and thumb hypoplasia [Figure 3]. Her vitals were normal. Her systemic examination showed hypogastric tenderness of the abdomen.

Figure 1: Short stature

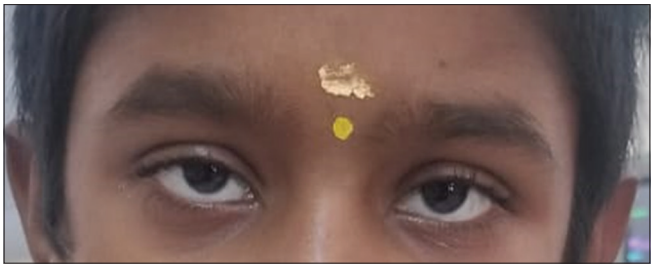

Figure 2: Partial ptosis

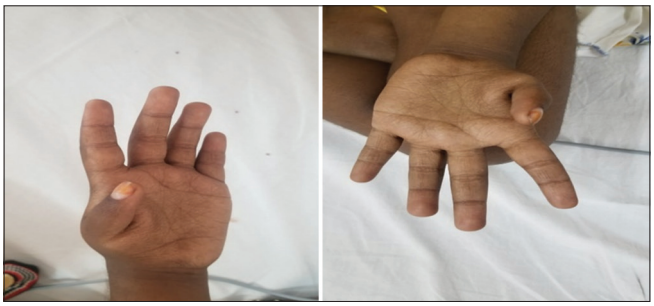

Figure 3: Thumb hypoplasia

On admission, the patient had no complaints of fever, cold, and breathing difficulty. Her birth history revealed that she was a full-term baby weighing 3 kg; delivered through lower segment cesarean section. She is the only child of healthy consanguineous parents. The child is immunized up to age. The patient had a surgical history of patent ductus arteriosus closure in the year 2013. She is a known case of FA which was diagnosed using bone marrow aspiration and biopsy on October 7, 2019, that showed markedly hypocellular bone marrow with reduced trilineage hematopoiesis. Further, the diagnosis was strengthened with peripheral smear examination which showed normocytic cells. No family members had experienced symptoms and manifestations that were similar to those of the patient. The treatment of choice for FA is HSCT. However, due to financial constraints, the patient is currently being treated with the drug Danazol 100 mg TDS, folic acid 5 mg OD and is on monthly blood transfusion (PRBC and platelet) since 2019.

Her complete blood counts disclosed that she had pancytopenia [Table1].

The patient's liver function test, renal function test, electrolytes, and urine analysis results were found to be unremarkable. Serum C-reactive protein (5.5 mg/dl) and serum amylase (189 U/L) levels were found to be elevated. Motion analysis test revealed that stool occult blood was positive. USG abdomen showed edematous wall thickening seen in distal small bowel loops, ileocecal junction, and cecum. Differentials considered were infective, neutropenic colitis.

Table 1: Complete blood counts

S. No.	Investigation	At the time of admission	At the time of discharge	Units of measurement
1.	Hemoglobin	2.7	10.1	g/dL
2.	RDW-CV	17.2	13.5	%
3.	HCT	8.1	30.1	%
4.	MCV	88	85	fL
5.	MCH	29.3	28.5	Pg
6.	MCHC	33.3	33.6	g/dL
7.	Platelet	7	14	10*3/ul
8.	Polymorphs	36.6	20.7	%
9.	Lymphocytes	50	66.5	%
10.	Monocytes	13.4	12.4	%
11.	Eosinophils	0	0	%
12.	Basophils	0	0.4	%
13.	WBC	1.34	2.75	10*3/ul
14.	RBC	0.92	3.54	10*6/ul

As conservative management, she was started on a broad-spectrum antibiotic (inj. meropenem 500 mg TDS, inj. pantoprazole 20 mg, inj. paracetamol 300 mg, inj. hyoscine butylbromide 10 mg, inj. ondansetron 2 mg, tab. tranexamic acid 250 mg, and inj. filgrastim 100 mcg). She was also supported with two units of PRBCs and two units of platelets. After transfusion, the patient was stable and was discharged.

DISCUSSION

FA is an autosomal recessive disorder which is an inherited form of aplastic anemia.[8] The prevalence of FA is about 4–7/ million live births. It is found in all the ethnic groups, but the rate is higher in the South African population, sub-Saharan Blacks, and Spanish Gitanos. Carrier frequency is more among Ashkenazi Jews of the United States, that is, one case/100 people with a birth rate of one case/30,000. It is common in both male and female.[5]

Majority of patients will have both physical anomalies and abnormal hematological findings. Apart from these, FA patients may also present with a phenotype characteristic of Seckel syndrome, Nijmegen breakage syndrome, Dubowitz syndrome, Holt-Oram syndrome, thrombocytopenia absent radius syndrome, Townes-Brocks syndrome, Saethre-Chotzen syndrome (TWIST1 mutation), velocardiofacial syndrome, Diamond-Blackfan anemia, and dyskeratosis congenital.[6] The most common features of FA are short stature and low birth weight, this can be attributed to superimposed endocrinopathies such as hypothyroidism, hypogonadism, infertility, growth hormone deficiency, and impaired glucose metabolism.[8] Multiple malformations, including skeletal and ear deformities, renal malformation, and abnormal skin pigmentation patterns, including café-au-lait spots and chromatosis, are the early manifestations of FA, due to the lack of specificity in these manifestations, it is often difficult to diagnose FA.[9] FA proteins are responsible for maintaining genomic stability, cell division integrity, and DNA repair mechanisms. Mutations in these genes will lead to chromosomal breakage, cell cycle disturbances, and increased rate of somatic mutations.[9] This genomic instability in patients with FA is characterized by hypersensitivity to DNA cross-linking agents such as diepoxybutane and mitomycin C resulting in chromosomal aberrations. Cell cycle analysis is an alternative diagnostic method used to discriminate between FA and non-FA individuals.[6]

In our case, the patient was presented with classical signs of FA; short stature, suboptimal weight, and pancytopenia early at the age of 5 years which was an advantage to initiate treatment. She also had congenital heart disease, partial ptosis, bilateral thumb hypoplasia, gum bleeding, and hypopigmented spots on both hands. Bone marrow aspiration and biopsy showed significantly hemodiluted and markedly hypocellular bone marrow. Hence, this case was diagnosed based on the above physical abnormalities, blood investigations, and bone marrow biopsy and aspiration.

Blood transfusion with PRBCs and platelets is one of the many supportive treatment options available for FA. Granulocyte colony-stimulating factors like filgrastim can be beneficial in neutropenic patients. Androgens stimulate the proliferation of hematopoietic stem cells, however, patients with severe bone marrow hypocellularity respond poorly to this therapy. The commonly used androgens are oxymetholone, danazol, and oxandrolone. Structural deformities in FA patients can be corrected with surgical treatments.[5] Novel gene therapy techniques have also been developed which involves the correction of CD4+ in affected cells and thereby replacing the abnormal gene by a normal gene.[2]

Since allogenic HSCT is the only proven long-term curative therapy available for the restoration of hematopoiesis, this treatment option is planned for our patient in the near future. FA can be detected by taking pre-emptive measures such as prenatal testing and family planning. Prenatal testing involves fetal ultrasonography evaluation, molecular genetic testing by amniocentesis or chorionic villous sampling, and chromosomal breakage testing.[10]

CONCLUSION

It is concluded that a greater suspicion is needed in diagnosing FA as unknown percentage of the patients manifest with non-specific symptoms. The clinical diagnosis of FA can be supported with the screening of FANCA gene; it helps in choosing the appropriate treatment plan along with suitable donors for HSCT. This child is on regular follow-up for blood transfusion and is being monitored for the signs of recurrent infection, bleeding, and anemic symptoms. As this is their first child, genetic counseling has been given to the parents. Careful surveillance for known complications, especially cancer and prompt intervention on their detection, has also contributed to the improved survival.

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