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Case Report

Fanconi anemia: in all its glory

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ABSTRACT

Fanconi Anemia (FA) is a rare autosomal recessive disorder affecting multiple body systems. The diagnosis is based on morphological abnormalities, hematological abnormalities (pancytopenia, macrocytic anemia & progressive bone marrow failure) and genetic testing. However, genetic testing is complicated for FA because there are often many genes that are associated with its development, and large duplications, deletions or sequence variations are frequently observed in some of these genes. We report a patient with cytogenetically confirmed Fanconi anemia. Although morphological abnormalities were present from birth, diagnosis was suspected and made at 8 years of age when he presented to us. We report this case to create awareness among clinicians to use modern modalities of diagnosis for such cases in addition to the clinical assessment. This would further help these children reach their adulthood with good quality of life.

Keywords: Fanconi anemia, Sprengel's deformity, Short stature, Absent thumb

INTRODUCTION

Fanconi Anemia (FA) is a rare genetic disorder characterized by progressive bone marrow failure,[1] variable congenital anomalies and a high predisposition to acute leukemia and other malignancies.[2] FA shows severe genetic heterogenicity, although the proteins encoded by FA-related genes are considered to work together in a common pathway that regulates cellular resistance to DNA cross-linking agents. At least 15 genes have been identified that are responsible for FA complementation groups: FANCA, FANCB, FANCC, BRCA2 (FANCD1), FANCD2, FANCE, FANCF, FANCG (XRCC9), FANCI, FANCM, BRIP1 (FANCJ or BACH1), FANCL, RAD51C (FANCO), and SLX4 (FANCP), PALB2 (FANCN).[3-5] Abnormalities of FA genes are inherited as autosomal recessive, except for FANCB mutations, which are inherited in an X-linked manner. Molecular diagnosis of FA is very complicated because at least 15 genes are associated with its development & the mutation spectra of most FA-associated genes are very diverse. Some of these genes frequently contain large deletions or duplications.[6]

CASE REPORT

An 8-year-old male presented with complaints of not gaining weight and repeated episodes of vomiting since one year. He was a full term, normally delivered child. Physical examination of the patient revealed microcephaly, short stature, triangular facies, epicanthal folds, wide nasal bridge, bat ears (Figure 1), hyperpigmented tongue (Figure 2), microglossia, micrognathia, Sprengel's deformity (Figure 3), absent right thumb (Figure 4), rudimentary left thumb (Figure 5), genu valgum and bilateral retractile testis. He had multiple café-au-lait spots on left shoulder (Figure 6), left arm and both thighs. His initial complete blood cell count results showed white blood cell: 3.5×10^9/L; hemoglobin: 5.5 g/dL; platelets: 29×10^9/L. Repeat hemogram indicated persistent thrombocytopenia. Peripheral smear showed macrocytic, normochromic erythrocytes. Bone

marrow aspiration revealed hypocellularity. Serum alfa-fetoprotein was high and thyroid profile was suggestive of hypothyroidism. Ultrasonography of abdomen and 2D-Echocardiography was normal.

A standard chromosomal breakage test with mitomycin-C (MMC) showed chromosomal hypersensitivity to the clastogenic agents. Mean number of breaks per metaphase, ratio of the mean number of breaks in patient/control per metaphase & the number of chromosome breaks per aberrant mitosis were higher than the normal range for non-FA cells.

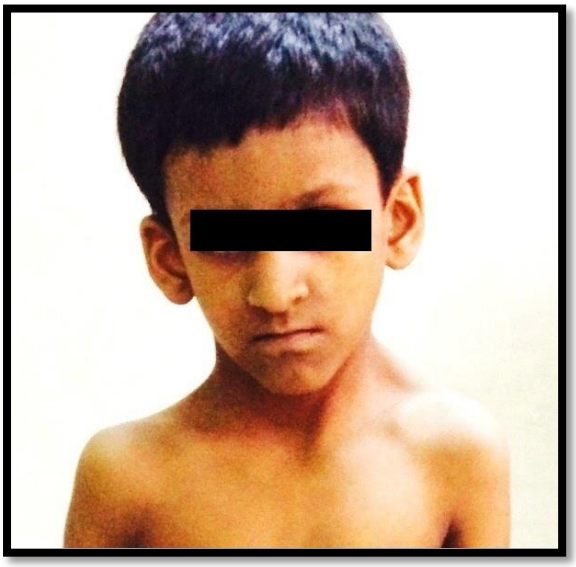

Figure 1: Showing triangular facies, microcephaly and bat ears.

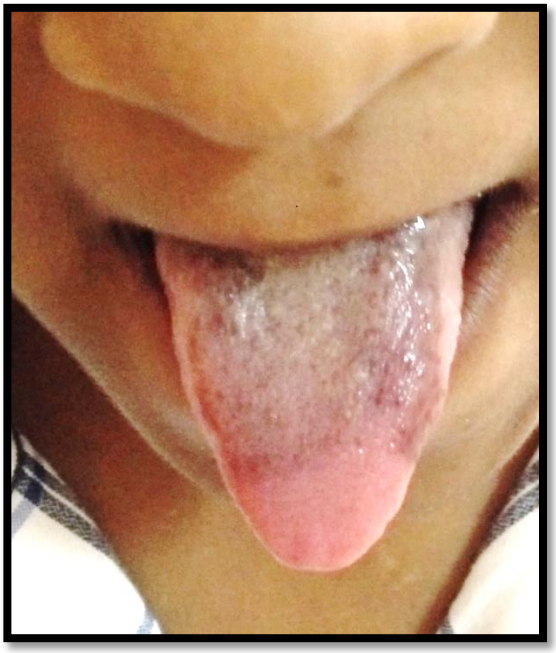

Figure 2: Hyperpigmented tongue.

Molecular analysis of FANCA gene revealed exon 4 to 7 deletion. The patient's clinical and cytogenetic findings were compatible with FA.

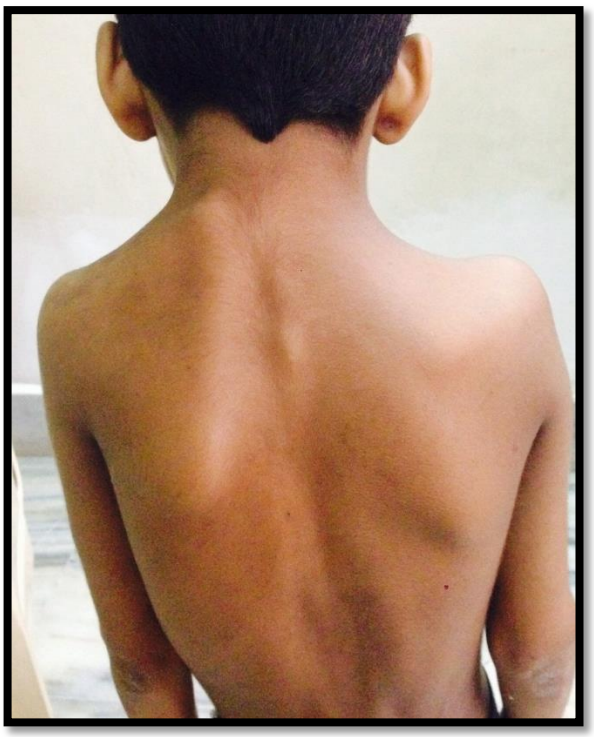

Figure 3: Sprengel's deformity.

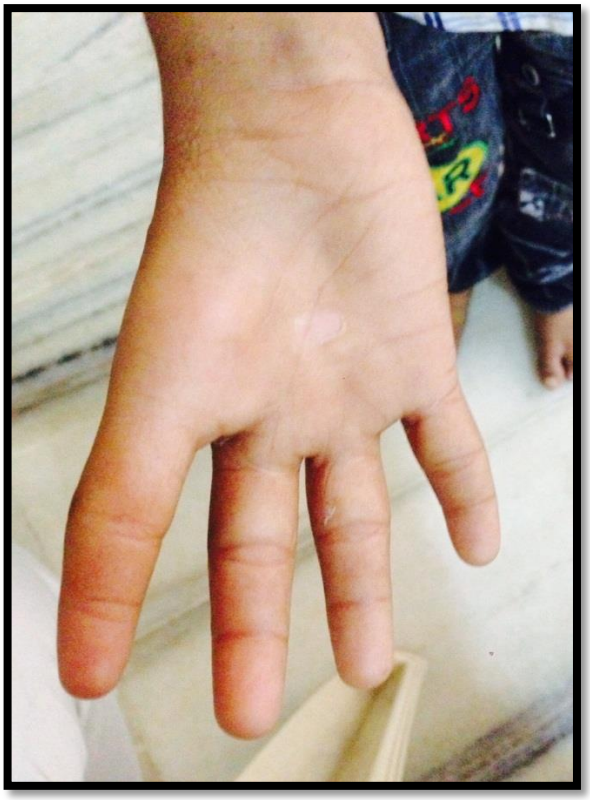

Figure 4: Absent right thumb.

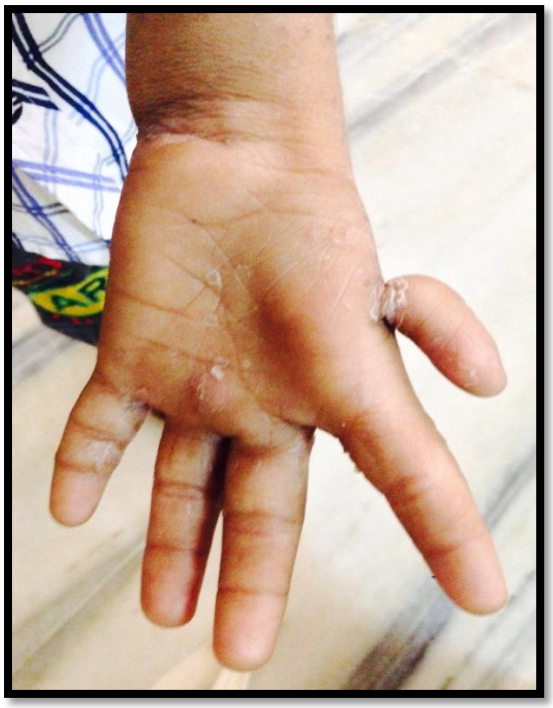

Figure 5: Rudimentary left thumb.

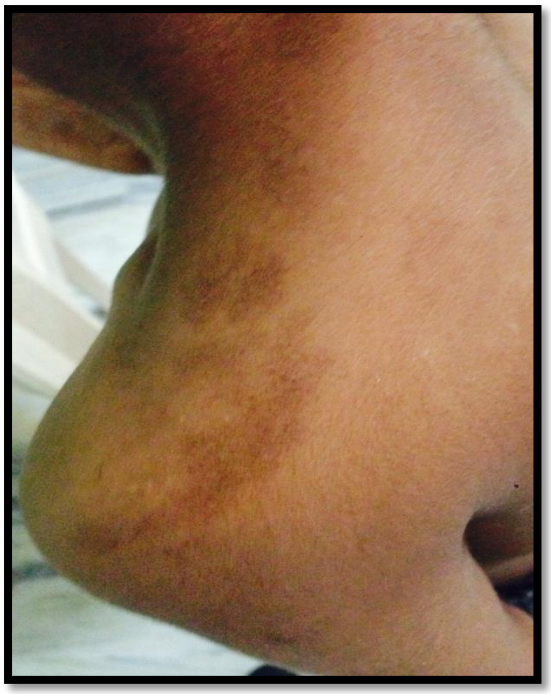

Figure 6: Multiple café-au-lait spots.

DISCUSSION

Fanconi anemia is inherited in an autosomal recessive manner. At presentation, patients with FA may have (1) typical physical anomalies but normal hematologic findings; (2) normal physical features but abnormal hematologic findings; (3) physical anomalies and abnormal hematologic findings. The later constitutes the classical phenotype (39 percent of cases). The most common anomaly in FA is hyperpigmentation of the neck, tongue and intertriginous areas, as well as vitiligo and café-au-lait spots. Half the patients have short stature. Growth failure may be due abnormal growth hormone secretion or with hypothyroidism. Absence of radii and anomalies of thumb which may be hypoplastic, supernumerary, bifid, or absent are common. Anomalies of the feet, congenital hip dislocation, and leg abnormalities are seen. A male patient with FA may have underdeveloped penis, hypospadias or phimosis; undescended, atrophic or absent testes. Many patients have a "Fanconi anemia facies" having epicanthic folds, abnormal shape, size, or position of the ears and microcephaly. Ectopic, pelvic, or horseshoe kidneys are detected by imaging. In addition it may show other organs as duplicated, hypoplastic or dysplastic. Cardiovascular and gastrointestinal malformations also occur. Approximately 10% of patients with FA are cognitively delayed.

FA can be diagnosed by bone marrow aspiration, chromosome breakage test, flow cytometry analysis & mutation screening.[7-10] A major feature of phenotype of FA is the propensity for cancer. Benign and malignant liver tumors (adenoma, hepatomas) are usually associated with androgen therapy for aplastic anemia.[11] Androgens are also implicated in the etiology of peliosis hepatis. Peliosis hepatis is reversible when androgen therapy is discontinued. 15 percent of patients with FA are at risk for acute leukemia or myelodysplastic syndrome.[12]

Hematopoietic stem cell transplantation is the only curative therapy for hematologic abnormalities. Androgens produce response in 50 percent of patients heralded by reticulocytosis[13] and a rise in hemoglobin within 1-2 months. Granulocyte Colony-Stimulating Factor (G-CSF) generally administered subcutaneously, improves the neutrophil count. Gene therapy, a theoretic possibility for the treatment of FA is presently at research stage only.

CONCLUSION

Diagnosis of FA requires high index of suspicion as it presents with physical abnormalities involving multiple organ systems. Early diagnosis of FA is very important as long term survival depends on the age of onset of various hematologic abnormalities and/or malignancies. If FA is recognized in the pre-anemic phase, drugs & environmental insults implicated in acquired aplastic anemia or malignancy can be avoided and life span can be prolonged with good quality of life. Early diagnosis also helps in planning of next pregnancy because the umbilical cord blood can be used for stem cell transplantation. Bone marrow or cord blood transplantation from an HLA identical sibling is now being considered as the treatment of choice for FA.

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