

Fanconi Anemia with Triphalangeal Thumbs, Syndactyly and Contractures of the Fingers in a 2 Year Old Boy

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KEY WORDS Fanconi anemia; syndactyly; contractures; triphalangeal thumbs; chromosomal breakage.

ABSTRACT Fanconi Anemia (FA) is a rare autosomal recessive disorder associated with pancytopenia, spontaneous chromosome instability and a variety of congenital anomalies. Hypersensitivity to bifunctional alkylating or DNA crosslinking agents like Mitomycin C (MMC), Diepoxybutane (DEB) and Nitrogen Mustard (HN₂) is used as a differential diagnostic test. A variable phenotype and age of onset of anemia make diagnosis difficult in some cases. We report a case of Fanconi anemia detected by the MMC stress test in a 2 year old boy, operated for bilateral syndactyly and contractures of fingers. He had a bifid thumb on the left hand and bilateral triphalangeal thumbs. There was no history of consanguinity or malformations, though a maternal uncle had a bifid thumb. USG in a subsequent pregnancy showed bony anomalies like scoliosis, talipes, contractures and radial aplasia, consistent with FA. The parents opted for termination. An early diagnosis of FA in a non-manifesting child would provide more time to explore different treatment options, since a delay in diagnosis could have serious consequences.

INTRODUCTION

Fanconi Anemia (FA) is a rare autosomal recessive disorder characterized by developmental defects of the thumb and radius, childhood onset of pancytopenic anemia usually between the ages of 5 and 9 and increased risk of leukemia (Fanconi 1967). Atleast five complementation groups (A-E) have been defined and the FAC gene has been cloned. Cells can be assigned to group C by direct mutation analysis (Jacobs et. al. 1997).

Since Fanconi's first report in 1927, the spectrum of phenotypic findings has greatly expanded. Patients may be severely affected with multiple congenital malformations or may have

a mild phenotype with no malformations. Affected individuals may exhibit varying degrees of low birth weight, growth retardation, abnormal skin pigmentation, hypoplasia or aplasia of the radius and thumbs, skeletal, renal and other anomalies. This phenotypic diversity makes differential diagnosis difficult in patients who exhibit few or no clinical features of FA other than bone marrow insufficiency (Auerbach et al. 1981).

Fanconi anemia is one of the well known chromosome instability syndromes. However, the study of spontaneous chromosome breakage is not always convincing (Dosik et al. 1979). Hypersensitivity to alkylating or DNA crosslinking agents like Mitomycin C (MMC), Diepoxybutane (DEB) and Nitrogen Mustard (HN₂) is therefore used as a standard laboratory assay to confirm the diagnosis (Howell et al. 1992). MMC is preferred as it is less hazardous.

We report a case of a child with minimal clinical features where a suspicion of FA prompted us to perform the Mitomycin C stress test and the diagnosis was confirmed before the onset of haematological changes.

CASE REPORT

A 2 year old Sindhi boy had bilateral syndactyly and contractures of the fingers. He was described as having 5-fingered hands instead of thumbs, by the parents. X-rays showed bilateral triphalangeal thumbs. He was operated earlier for syndactyly and contractures. He had a bifid thumb on the left hand which was also said to be present in a normal maternal uncle. Post operative pictures of the hands are shown in Figure 1. The child was born of a non consanguineous marriage. He was the first child. The mother had two subsequent abortions and was pregnant

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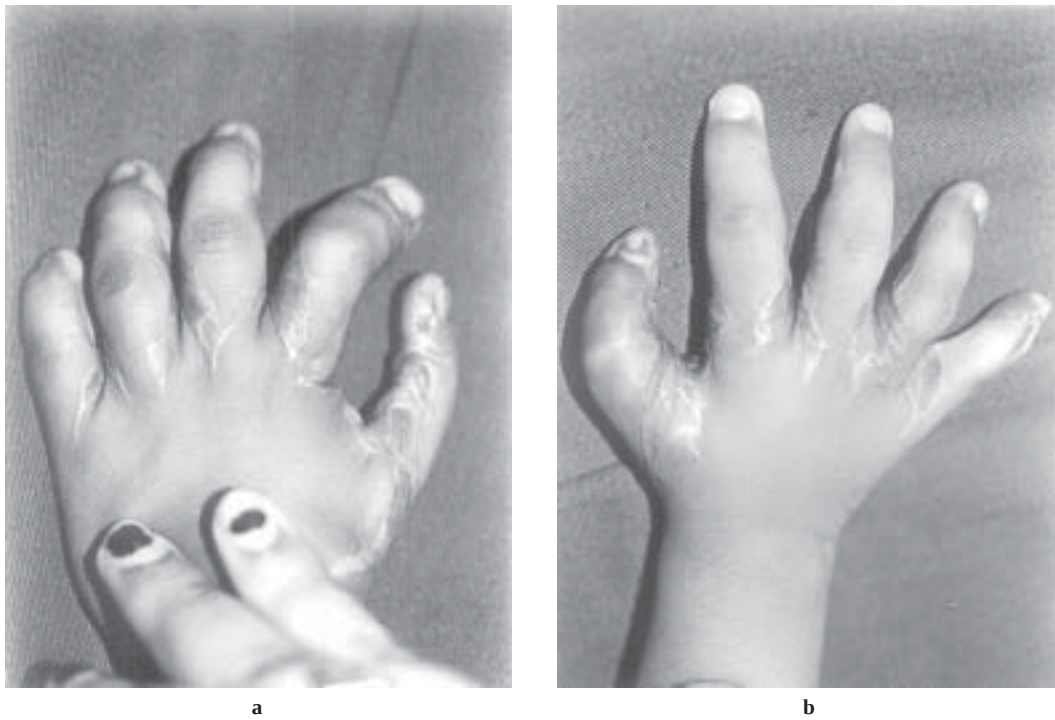


Fig. 1. (a-b) Post operative pictures of the hands of the patient, showing bilateral triphalangeal thumbs

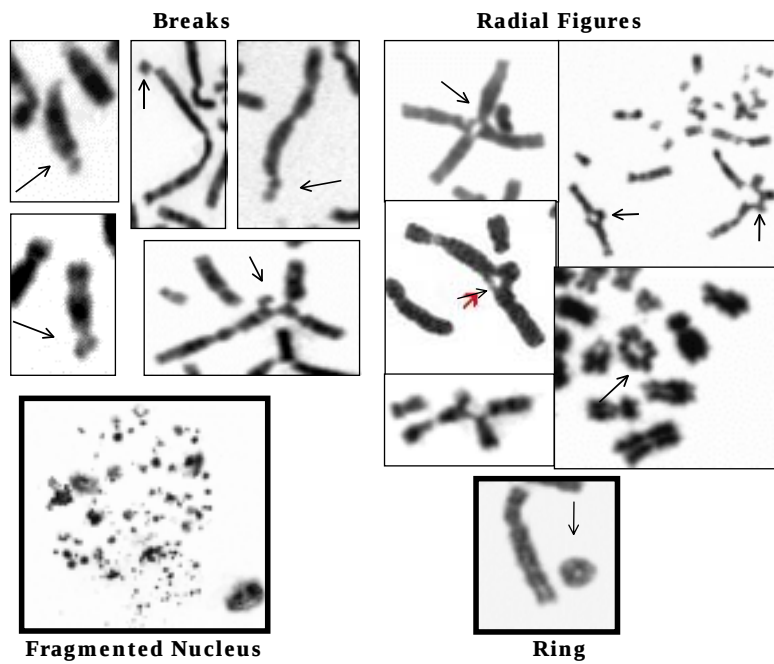


Fig. 2. Chromosome abnormalities seen in the MMC treated cultures

again. They came to our department to rule out the possibility of a second affected child. Fanconi anemia was suspected in the proband because the thumbs were involved. Mitomycin C stress test confirmed the diagnosis.

A second trimester 3D ultrasonography of the ongoing pregnancy showed bony abnormalities like scoliosis, contractures of the limbs and talipes, though the fingers were apparently normal. Such bony abnormalities and contractures are known to be associated with Fanconi anemia. The parents opted for termination of pregnancy in their hometown.

MATERIAL AND METHODS

For diagnosis of Fanconi anemia, the Mitomycin C stress test (Cervenka et al. 1981) was carried out. Multiple lymphocyte cultures of the patient, parents and control were set up. MMC was added at final concentrations of 20, 50 and 80ng/ml while planting. Cultures were incubated for a period of 96 hours. Cultures without MMC served as internal controls. Harvesting and slide preparation were according to standard protocols. Banded and unbanded slides were stained with Geimsa. The percentage of chromosomal breaks and radial figures was calculated for every culture.

OBSERVATIONS

The percentage of breaks and radials increased sharply in the child at the highest dose of MMC. 88% breaks and 10% radials were observed in cultures at a final concentration of 80ng/ml compared to 38% breaks and 2% radials in his parents. The percentage of breaks and radials in all the cultures is given in table 1. The number of fragmented nuclei was also high in the patient as compared to controls. Figure 2 shows the chromosome abnormalities seen in the patient. The G-banded karyotype of the child was normal.

DISCUSSION

Triphalangeal thumbs noted in the present case are very rare. Radial ray defects and associated anomalies also occur in other syndromes like Holt-Oram, TAR (thrombocytopenia – absent radius) and VATER sequence (Cox et al.

Table 1: Percentage of breaks and radials seen with different concentrations of MMC

MMC final concentration	Patient	Father	Mother	Control
Nil				
% Breaks	3	2	0	1
% Radials	0	0	0	0
Metaphases	100	100	50	100
20 ng/ml				
% Breaks	19	16	18	15
% Radials	2	0	1	0
Metaphases	125	125	154	150
50 ng/ml				
% Breaks	68	35	16	59
% Radials	8	2	4	6
Metaphases	167	135	55	65
80 ng/ml				
% Breaks	88	33	43	37
% Radials	10	2	2	6
Metaphases	42	55	51	51

1989). Cytogenetic analysis helps in differential diagnosis especially in cases of FA without congenital malformations (Giampietro et al. 1997).

An accurate diagnosis of FA is very important for therapeutic planning of these patients. Androgen therapy with or without additional steroids is the therapy of choice in proven cases of FA, because of the inherent chromosomal aberrations (Athale et al. 1991). Bone marrow transplants are carried out in those who are refractory to androgens. However, FA patients require reduction in the usual dosage of drugs in the pre-transplant conditioning regimen as well as during treatment of malignancies with chemotherapeutic agents. Since they are hypersensitive to all DNA crosslinking agents, high dose chemotherapy and irradiation routinely used in idiopathic aplastic anemia may be lethal in Fanconi anemia.

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