Case Report

Aromatase excess syndrome presenting with prepubertal gynecomastia in an Egyptian child with type 1 neurofibromatosis

Kotb Abbass Metwalley, Hekma Saad Farghaly

Department of Pediatrics, Assiut University, Assiut, Egypt

A romatase excess syndrome (AEXS) is a rare autosomal dominant disorder characterized by prepubertal gynecomastia, it responds well to medical treatment. In the absence of prompt suspicion, it can expose the patient to the risk of unnecessary surgical intervention. Up to our best knowledge, the association between AEXS and neurofibromatosis type 1 (NF1) was not reported before. Here, we describe a AEXS presenting with prepubertal gynecomastia in an Egyptian child with NF1 that improved with aromatase inhibitors.

Key words: Aromatase excess syndrome, neurofibromatosis, prepubertal gynecomastia

Introduction

Gynecomastia is defined as the presence of excessive breast tissue in males, which can appear unilateral or bilateral. Bilateral gynecomastia is frequently found in the neonatal period, early in puberty, and with increasing age.[1] Most of recoded cases of gynecomastia in children with neurofibromatosis type 1(NF1) are due to pseudoangiomatus stromal hyperplasia, lipomatous, or neurofibromatous proliferations of the mammary region or as hamartomatous lesions of nerves and their supporting stroma.[2] Aromatase excess syndrome (AEXS) is a rare, hereditary, autosomal dominant disorder caused by mutations in the CYP19A1 gene which encodes aromatase AEXS is characterized by increased production of estrogen and decreased testosterone (T) level. It is presented with pre- or peripubertal onset gynecomastia, gonadal dysfunction, advanced bone age from childhood to pubertal period, and short adult height in affected males.[3] To the best of our knowledge, this is the first case of gynecomastia in a 4-year-old Egyptian boy with NF1 caused by AEXS.

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Case Report

A 4-year-old Egyptian boy was referred to our clinic for evaluation of bilateral asymmetrical gynecomastia which slowly increased in size over the past 6 months. He was known to have NF1, but had no other medical history of note. Family history was negative for breast malignancies, but positive for NF1 in the father and prepubertal gynecomastia in two of his brothers. Mental development was normal. No drugs or dermal applications were used. There was no history of galactorrhea. Physical examination showed a healthy-appearing boy with multiple café-au-lait spots with diameter > 1.5 cm [Figures 1 and 2]; axillary and inguinal freckling. His height was 115 cm (>97th percentile) and weight 20 kg (90th percentile).

Palpation of the both breast revealed a firm mobile mass measuring approximately 6 cm in diameter in left and 4 cm in the right corresponding to a female Tanner B3 stage[4] [Figure 3], with tenderness on deep palpation. The right

Address for correspondence: Asst. Prof. Kotb Abbass Metwalley, Department of Pediatrics, Pediatric Endocrinology Unit, Assiut University, Assiut, Egypt. E-mail: kotb72@yahoo.com

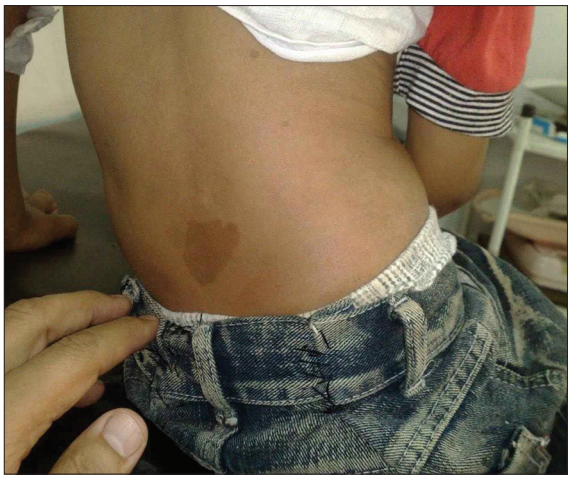

Figure 1: Café-au-lait spots on the back of the reported child

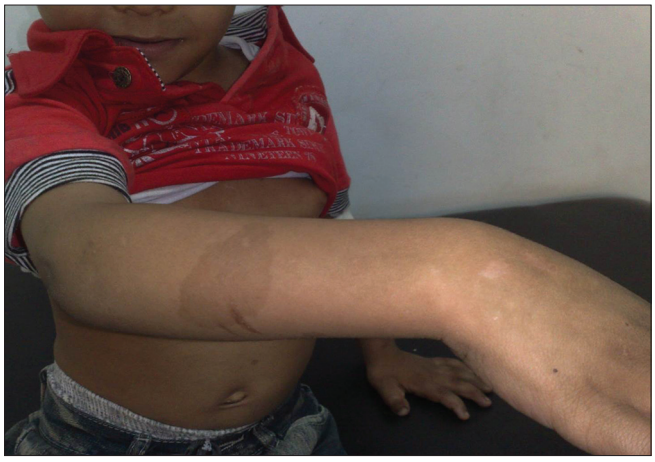

Figure 2: Café-au-lait spots on upper limb of the same child

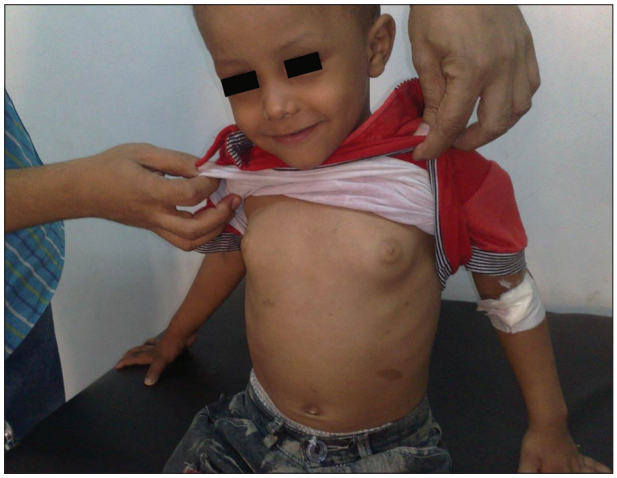

Figure 3: Bilateral asymmetrical gynecomastia of the same child

nipple-areola complex was also enlarged, measuring 1.5 cm compared to 1 cm on the left. There was no sign of galactorrhea and his testicular volume was 4 ml bilaterally. The penis was infantile and there was no pubic or axillary hair. Ultrasound examination of both breast showed retroareolar glandular tissue with normal aspects and swelling containing subcutaneous fat tissue. Bone was advanced by 3 years.[5] An abdominal and testicular computed tomography scan excluded any estrogen-producing tumor. Routine serum/blood chemistry was normal. Chromosome analysis in cultured peripheral blood lymphocytes was also normal. Endocrinological testing revealed that the child had persistently raised levels of estradiol (E2; 33, 40, and 37 pmol/l; normal: 15–35) in the presence of undetectable T levels of < 0.1 nmol/l (9.1–27.8). Basal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were normal (0.5 and 0.41 IU/l, respectively and 1.3 and 1.5 IU/l, respectively), with no change in response to stimulation by 100 mg of LH-releasing hormone intravenously. TSH, free thyroxine (FT4), and prolactin levels were normal. Genetic studies showed mutations of the CYP19A1 gene and presence of the allele (TTTA) 11 in a homozygous state and located in intron 4 of the CYP19A1 gene. Based on these findings, a diagnosis of AEXS was made. He was started on treatment with an aromatase inhibitor (tamoxifen 10 mg/day, orally). Our patient was seen 6 months after starting treatment. His growth velocity decreased from 7 to 5 cm per year and gynecomastia from 6 to 3 cm in diameter. E2 and T levels were near to normal levels. Our plan is to continue treatment and to follow-up every 6 months till improvement of gynecomastia.

Discussion

Some breast development occurs in 30-65% of boys during puberty, but is extremely uncommon in the prepubertal years.[6] Prepubertal gynecomastia is most frequently caused by exogenously administered estrogens, hormone-secreting or local tumors, and rarely by AEXS.[7] In boys, AEXS can lead to gynecomastia, while in girls it can lead to precocious puberty and gigantomastia. In both sexes, early epiphyseal closure leads to short statue.[3] Aromatase, also known as estrogen synthetase, is the key enzyme in estrogen biosynthesis. The enzyme, localized in the endoplasmic reticulum of the estrogen-producing cell, is encoded by the CYP19A1 gene. It catalyzes the conversion of 4-androstendione (A) into estrone (E1) and that of T into E2.[8] AEXS has been

correlated to serum estradiol and E1 excess. It was first reported in a boy with prepubertal gynecomastia in 1977,[9] then in five members of an African-American kindred in 1985.[10] This in agreement with our index case who had raised E2, low T levels, advanced bone age, and positive family history of prepubertal gynecomastia. These findings suggested a diagnosis of AEXS which was confirmed by molecular genetic study.

Children with the AEXS had greatly advanced bone age which was report in our index case; the degree of skeletal maturity was disproportionate to height (chronological age < height age < skeletal age) despite accelerated growth. This situation is seen frequently in untreated precocious puberty, when the rate of skeletal maturation overcomes linear growth.[11] These children are potential to have short stature during adult life due to potent effect on estrogens on accelerating premature epiphyseal closure.[3] Considering the important role that aromatase plays in the production of elevated quantities of estrogen in males with gynecomastia, it would be anticipated that aromatase inhibitors (tamoxifen) would have been a mainstay in the therapy of the disorder.[12] Aromatase inhibitors effectively delay epiphyseal maturation and improve both estrogen and T levels our index case.

NF1 is a common human genetic disease with an incidence of about 1 in 3300, autosomal dominant mode of inheritance, and characterized by localized overgrowth of mesodermal and ectodermal tissues.[13] Our index case fulfills the NF1 criteria by presence of multiple café-au-lait spots with diameter > 1.5 cm axillary and inguinal freckling and NF1 in his father. Gynecomastia associated with NF1 include pseudoangiomatus stromal hyperplasia, lipoma, neurofibroma, hamartomal primary malignant schwannoma, a cystosarcoma phylloides, and carcinomas, have been reported in the medical literature.[14] All above condition are indications for biopsy and surgical treatment, hormonal assay of these cases are unremarkable.

Conclusions

Prepubertal gynecomastia could be a sign of possible underlying diseases, a thorough examination and investigation is recommended to reach a diagnosis hormonal assay is recommended in every child with prepubertal gynecomastia even in children with neurofibrmatois before going to biopsy and surgery. Since such a diagnostic investigation is complex, it should best be done by an experienced endocrinologist.

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