The association of Klinefelter syndrome and multiple pterygium syndrome: an unusual presentation

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SUMMARY: Nur BG, Altıok-Clark Ö, Toylu A, Lüleci G , Mıhçı E. The association of Klinefelter syndrome and multiple pterygium syndrome: an unusual presentation. Turk J Pediatr 2013; 55: 559-563.

Multiple pterygium syndrome is characterized by a number of phenotypic features, small stature, webbing of the neck, elbows, and/or knees, and joint contractures. In this report, we present an 11-year-old boy who had the classical findings of multiple pterygium syndrome, and his chromosomal analysis revealed a 47,XXY karyotype. Interestingly, he did not show any of the main clinical signs of Klinefelter syndrome. This patient appears to be the first reported case in the literature in which a non-mosaic 47,XXY karyotype has been found in a patient with multiple pterygium syndrome. The aim of the present report is to describe a non-classic Klinefelter syndrome associated with multiple pterygium syndrome and to emphasize the importance of karyotype analysis in patients with multiple pterygium syndrome.

Key words: Klinefelter syndrome, multiple pterygium syndrome, karyotype analysis, short stature.

Klinefelter syndrome is the most common sex chromosome disorder, with a prevalence of one in 1000 males[1]. The most widespread karyotype observed among affected patients is 47,XXY. In addition to the 47,XXY karyotype, a number of other karyotypes have also been observed in patients with Klinefelter syndrome, including 46,XX in males, 47,XXY in females, 47,XX,der(Y), 47,X,der(X),Y, and other numeric sex chromosome abnormalities (48,XXXY, 48,XXYY, and 49,XXXXY). Theoretically, 50% of XXY cases could arise from an error during paternal meiosis I, and the remainder could occur during maternal meiosis I or II[2]. Klinefelter syndrome is not easy to diagnose in children due to the absence of significant manifestations before puberty. The typical symptoms are a tall stature, narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, azoospermia, androgen deficiency, and normal to slightly decreased verbal intelligence. In addition, osteoporosis, thromboembolic disease, diabetes mellitus, and an increased risk for developing cancer have also been observed[3].

The pterygium syndromes are a clinically heterogeneous group of entities (classified as at least 15 different entities), of which the multiple pterygium syndrome is one of the most frequently observed. It is a rare condition, characterized by multiple congenital joint contractures and multiple skin webs. Multiple pterygium syndrome is generally transmitted by an autosomal recessive pattern of inheritance; however, autosomal dominant or X-linked dominant inheritance patterns have also been described[4-6].

In this report, we present an 11-year-old male who showed the typical characteristics of multiple pterygium syndrome. Chromosomal analysis revealed a non-mosaic 47,XXY karyotype. Interestingly, he did not show the main clinical signs of Klinefelter syndrome.

Case Report

An 11-year-old male was admitted to our hospital due to short stature, limited movement of his joints, curvature of the waist, and bilateral congenital hip dislocation. He was born in the 36th week of gestation, weighing 2800 g. He was the first-born child from a marriage between first cousins. He was delivered by cesarean section due to a breech presentation. The findings of the prenatal

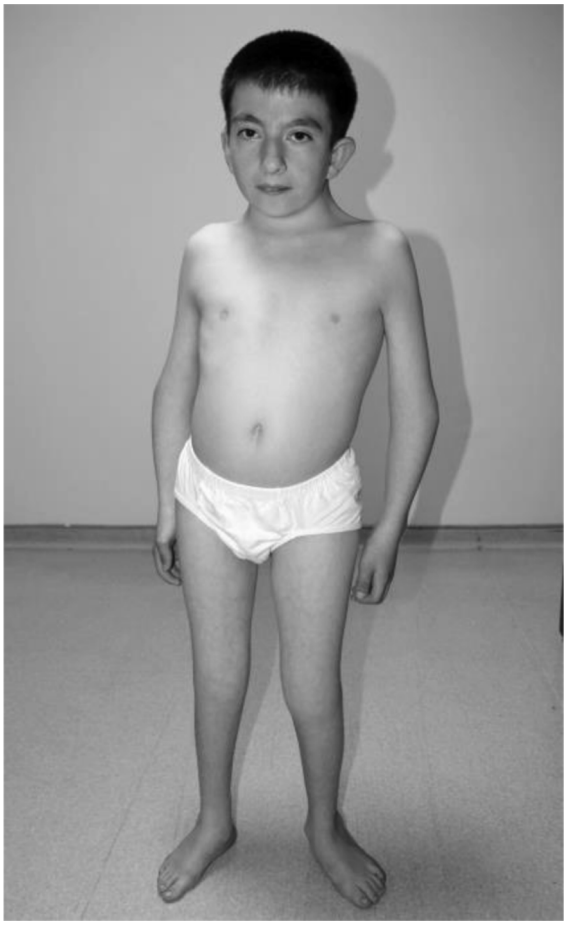

Fig. 1. Proband showing short stature, dolichocephaly, low-set ears, pterygia of the neck and elbow, inverted nipples, scoliosis, and patellar and foot deformities.

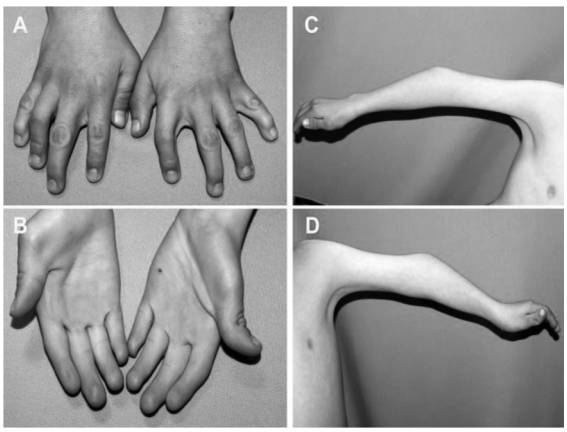

Fig. 2. A: Dorsal view of the hands showing marked camptodactyly and slight cutaneous syndactyly of the 2nd, 3rd and 4th fingers and clinodactyly of the 5th finger. B: Volar surface of the hands showing pterygia of the fingers and absence of flexion creases. C-D: Axillary and elbow pterygia.

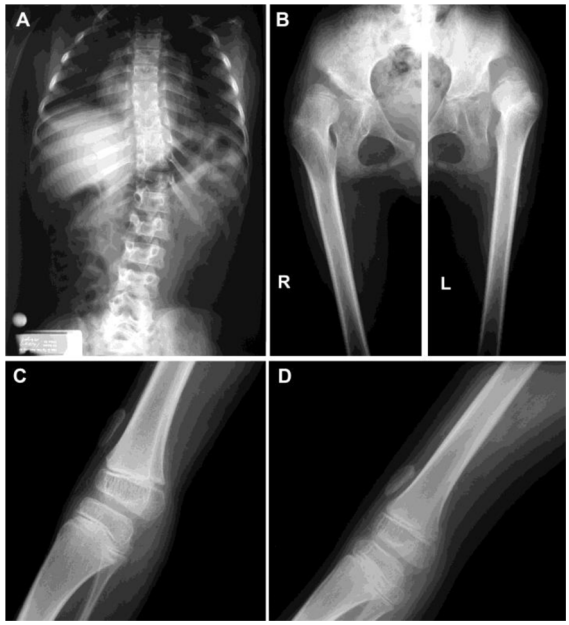

Fig. 3. A: Anteroposterior chest image showing scoliosis. B: Bilateral hip image showing dislocation of the hip. C: Lateral radiography of the right knee. D: Lateral radiography of the left knee showing dislocation of the patella.

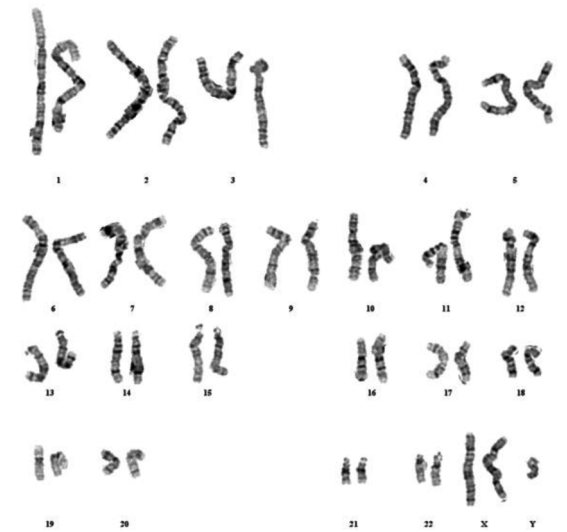

Fig. 4. G-banded karyogram of the patient showing a 47,XXY karyotype.

ultrasound examination (which was performed at an outside medical center) were normal. His mother was healthy, 28 years old, and gravida 4, para 2; her two prior pregnancies had both ended in miscarriages in the first trimester. At five years of age, he underwent surgery for a foot deformity, bilateral cryptorchidism and a bilateral inguinal hernia.

On the physical examination, his weight was 23 kg (<3rd centile), height 122 cm (<3rd centile), and head circumference 48 cm (<3rd centile). He had a facies with a downslanting palpebral fissure, thick eyebrows, ptosis of the eyelids, bilaterally low-set ears, an anteverted left ear, high-arched palate, tubular nose, crowded teeth, microretrognathia, a low-set hair line, and dolichocephaly. In addition, he also had webbed neck, bilaterally inverted nipples, pectus excavatum, pterygia of the axilla, scoliosis, camptodactyly, clinodactyly, absence of finger crisis, limited movement of the knees and ankles, bilateral dislocation of the hip, genu valgum, pes cavus deformity, rocker bottom feet, and overriding of 2nd and 3rd toes (Figs. 1, 2 A-D). Neither gynecomastia nor genital hypoplasia was observed. His scores on the Wechsler Intelligence Scale for Children-R were as follows: 72 on the verbal intelligence quotient, 73 on the performance intelligence quotient, and 70 on the full scale intelligence quotient.

The results of the biochemistry tests for skeletal assessment and short stature were as follows: calcium: 9 mg/dl (normal [N]: 8.8-10.8), phosphorus: 5.2 mg/dl (N: 2.5-4.5), alkaline phosphatase: 178 IU/L (N: <300), parathyroid hormone: 29 pg/ml (N: 15-65), and 25-OH vitamin D: 13.5 ng/ml (cut-off for vitamin D insufficiency: 20). His testicular volumes and testosterone and gonadotropin levels were consistent with normal pre-pubertal levels. His skeletal age was found to be normal for age. A radiological examination of the chest and the spine revealed the presence of thoracolumbar scoliosis; however, no evident costal defects were detected. Radiography of the hands revealed osteoporosis, and bilaterally short and broad metacarpal bones. Furthermore, the hip image showed a bilateral hip dislocation, and lateral radiography of the knees showed dislocation of the patella (Fig. 3 A-D). Dual-energy X-ray absorptiometry (DEXA) revealed the presence of osteopenia (lumbar Z-score: -0.8, femur Z-score: -2.9). Echocardiography detected both a secundum atrial septal defect and a muscular ventricular septal defect. The results of an ophthalmologic examination, renal ultrasonography, and cranial magnetic resonance imaging were all found to be normal. Chromosomal analysis performed on cultured leukocytes using GTG banding techniques showed a 47,XXY karyotype based on the 20 metaphases analyzed (Fig. 4).

Discussion

The multiple pterygium syndromes are a phenotypically and genetically heterogeneous group of syndromes, and have traditionally been divided into prenatally lethal and non-lethal types. The typical features of these syndromes are growth retardation and multiple pterygia involving the neck, fingers, and antecubital, popliteal, and intercrural areas. Downslanting palpebral fissure, epicanthal folds, ptosis of the eyelids, puffiness around the eyes, low-set ears, and micrognathia are the typical facial features of these syndromes. Congenital heart defects have been found in approximately 25% of patients[7]. Our patient showed the characteristic features of a non-lethal type of multiple pterygium syndrome, with the facial features, short stature, hypoplastic nipples, webbed neck, skin webs across the joints, multiple congenital joint contractures, camptodactyly, foot deformities, scoliosis, congenital hip dislocation, cryptorchidism, and congenital heart defects that are commonly associated with this syndrome. While karyotypic analysis was consistent with that of a non-mosaic Klinefelter syndrome, our patient differed both phenotypically and cognitively from what would be expected with Klinefelter syndrome. The features typically observed in a patient with Klinefelter syndrome are a tall stature with eunuchoid body proportions, hypogenitalia, learning disabilities, and problems with language. However, our patient had no learning disabilities, and his language and cognitive levels were normal.

Chromosomal abnormalities have been reported rarely in a patient with multiple pterygium syndrome. One instance, however, was a 47,XXY/48,XXXY mosaicism in association with joint webbing of the bilateral cubital and popliteal regions, aniridia, mental retardation, bilateral cataracts, exophthalmia, and glaucoma. Another such case was found to have a translocation between chromosomes 6/7 t(6:7)(q15;32) in association with pterygia of the neck, axilla, cubital fossa, wrists, and popliteal region, cutis laxa, and a bilateral absence of the lacrimal gland[8,9]. Furthermore, XY gonadal dysgenesis has also been described

in association with multiple pterygium syndrome[10]. Non-mosaic Klinefelter syndrome in association with multiple pterygium syndrome was first described in a fetus by Lembet et al.[11] In that instance, multiple joint contractures were detected in the 16th week of gestation and the pregnancy was later medically terminated. A subsequent fetopsy led to the diagnosis of multiple pterygium syndrome, and amniocentesis revealed a 47,XXY karyotype. Eventually, the association between multiple pterygium syndrome and Klinefelter syndrome was reported in the previous two cases, and this condition may have an explanation rather than being just coincidental. There was an increased incidence of musculoskeletal disorders in Klinefelter syndrome, such as pes planus, asymmetric hip rotation, clinodactyly, and radioulnar synostosis. Sprouse et al.[12] reported that 85% of Klinefelter syndrome patients had generalized hypotonia. They reported that the hypotonia affects gross motor development, and observed that tonus was decreased in the trunk, extremities, and facial muscles. Although the pathogenesis of lethal multiple pterygium syndrome remains unclear, primary aplasia of developing muscle fibers, abnormally fragile collagen, and fetal a/hypokinesia have all been suggested as possible pathogenic mechanisms[13-15]. Hypotonia has been thought to be involved in the etiology of contractures and could be responsible for those observed in our patient as well.

In our patient, multiple pterygium syndrome appears to have been transmitted by an autosomal recessive (Escobar type) or X-linked recessive trait due to the consanguinity of the healthy parents and the two prior spontaneous abortions. These heritability patterns are usually associated with lethal-type multiple pterygium syndrome[16]. The fetus that was reported by Lembet et al. to have both Klinefelter syndrome and a suspected lethal-type multiple pterygium syndrome had no hydrops. They speculated that the lethal phenotype was suppressed by X-inactivation, and hypothesized a process of lyonization that caused inactivation of an excess of mutation-bearing X chromosomes, thus preventing the lethal phenotype[11].

It is important to note, however, that various phenotypic abnormalities and X-linked or autosomal recessive diseases have been reported in association with Klinefelter syndrome[17,18]. While a short stature is frequently seen in multiple pterygium syndrome, it is only rarely observed in Klinefelter syndrome. In instances in which a short stature is observed in Klinefelter syndrome, it has been reported that it is due to idiopathic renal tubular acidosis, growth hormone deficiency, or X-linked hypophosphatemic rickets[19-22].

Osteoporosis is present in one-fourth of Klinefelter syndrome patients[23,24]. In childhood and at the beginning of puberty, young patients with Klinefelter syndrome have normal bone density. During the later stages of puberty, however, they develop progressive testicular failure that leads to primary hypogonadism, and this represents the most important risk factor for reduced bone mass and osteoporosis. Although our patient is prepubertal, we still detected decreased bone mass. In our patient, this decreased bone mass may be explained by a combination of contributing factors, including relative inactivity due to limited movement of joints, disuse of the lower limbs owing to his operation and patella dislocation, an unfavorable fat:muscle ratio, lack of sun exposure, and the resulting vitamin D deficiency.

In the differential diagnosis, care should be taken to distinguish multiple pterygium syndrome from femoral hypoplasia-unusual facies syndrome, Noonan syndrome, Turner syndrome, Leopard syndrome, craniocarpotarsal dysplasia, and fetal akinesia sequence[7]. Additionally, a patient such as ours should be distinguished from popliteal pterygium syndrome, in which the pterygium is limited to the popliteal region. The congenital dislocation of the patella manifests itself in the form of flexion contracture of the knee, genu valgum, external tibial torsion, and delayed walking. Patellar dislocations associated with Down syndrome, nail-patella syndrome, Kabuki syndrome, and Ellis-Van Creveld syndrome have all been reported previously, but no association has yet been established between congenital patellar dislocations and multiple pterygium syndrome or Klinefelter syndrome[25]. A bilateral patellar dislocation (patella alta or high-riding patella) was detected in our patient, and may be a condition that is only rarely associated with multiple pterygium syndrome.

Based on an extensive search of the literature,

this appears to be the first report of a patient with a non-mosaic 47,XXY karyotype in association with multiple pterygium syndrome. Although multiple pterygium syndrome is very rare, it is important to perform a karyotype analysis in order to rule out chromosomal abnormalities. An increased awareness of multiple pterygium syndrome may aid in an early diagnosis, which in turn allows for more effective treatment and genetic counseling.

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