Neurofibromatosis with Vulvar Involvement and Retarded Sexual Development: A Case Report

GECİKMİŞ SEKSÜEL GELİŞİMİ VE VULVAR TUTULUMU OLAN NOROFIBROMATOZİS: VAKA TAKDİMİ

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SUMMARY

Objective: *To present a rare from of neurofibromatosis involving the vulva, skeletal system and causing hypogonadotropism and the literature review about it.*

Institution: *This study was held in Ankara Dr.Zekai Tahir Burak Women's Hospital.*

Material and Method: *A 19 year old girl who applied to our Reproductive Endocrinology Clinic with a history of breast underdevelopment and a left vulvar mass.*

Results: *Vulvar mass was found to be a neurofibroma. Whole body X-rays revealed cysts at long bones and a deviated coccyx. This patient was found to have estradiol and gonadotrophins in hypogonadotrophic range.*

Conclusion: *What interesting is that this hamartamatous disorder, which arises from neural crest and has been described by von Recklinghausen in 1882 first, is different from this particular case where retarded sexual development occurs, usually appears as precocious puberty. As this patient has hypogonadotropism, she is under hormone replacement treatment, until she may have infertility problems. As the patient was considered a neurofibromatosis case (pelvic and skeletal involvement) with hypogonadotrophism (which occurs very rarely), she is now under periodic control for the risk of malignant degeneration.*

Key Words: Neurofibromatosis, Vulvar enlargement, Retarded sexual development

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ÖZET

Amaç: *Nörofibromatozis hastalığının vulvayı, iskelet sistemini içine alan ve hipogonadotropizme neden olan seyrek bir tipi ve bu konudaki literatür derlemesi sunmak.*

Çalışmanın yapıldığı yer: *Ankara Dr.Zekai Tahir Burak Kadın Hastanesi.*

Materyel ve Metod: *Reprodüktif Endokrinoloji Kliniğimize başvuran 19 yaşında, göğüslerde gelişme geriliği ve sol vulvada kitlesi olan bir genç kız.*

Bulgular: *Vulvadaki kitlenin patolojik incelenmesi neurofibrom olduğunu gösterdi. Ayrıca vücut röntgenleri uzun kemiklerde kistler ve eğri bir koksiks saptadı. Estradiol ve gonadotropinleri hipoganodotropik limitlerdeydi.*

Sonuç: *Bu konuda ilginç olan şudur ki nöral çıkıntıdan köken alan, ilk olarak 1882'de von Recklinghausen tarafından bildirilen bu hamartomatöz bozukluk, bildirilen vakadan farklı olarak genelde geri kalmış seksüel gelişme yerine erken puberteye neden olmaktadır. Bu hasta hipogonadotropizmle (seyrek olarak görülür) birlikte neurofibromatozis (pelvik ve iskelet tutulumu mevcut olan) olarak kabul edildiği için malign dejenerasyon yönünden kontrol altındadır.*

Anahtar Kelimeler: Nörofibromatozis, Vulvada şişkinlik, Geri kalmış seksüel gelişim

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We are reporting a rare variation of neurofibromatosis with vulvar, skeletal involvement and hypogonadotropism with the literautre review on this subject. What interesting is here that this hamartomatous disorder of neural crest derivation which was first described by von Recklinghausen in 1882, occurs usually causing precocious puberty rather than retarded sexual development unlike the case presented here.

Familial neurofibromatosis or von Recklinghausen's disease is a Mendelian dominant hereditary disorder manifested by café au lait spots of increased skin pigmentation and multiple neurofibromas arising from neurilemmal sheets of the peripheral nerves, most frequently along the main nerves on the flexer aspects of the limbs, hands, neck, head, tongue, face and stomach. Involvement of the external genitalia is rare. Usually urogenital neurofibroma is a local manifestation of von

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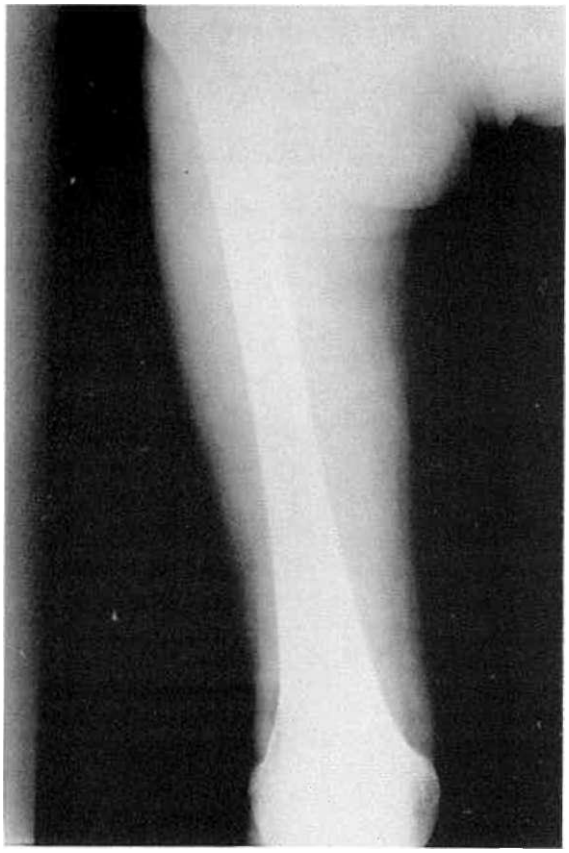

Figure 1a. Cortical cyst at right femur distal lateral part.

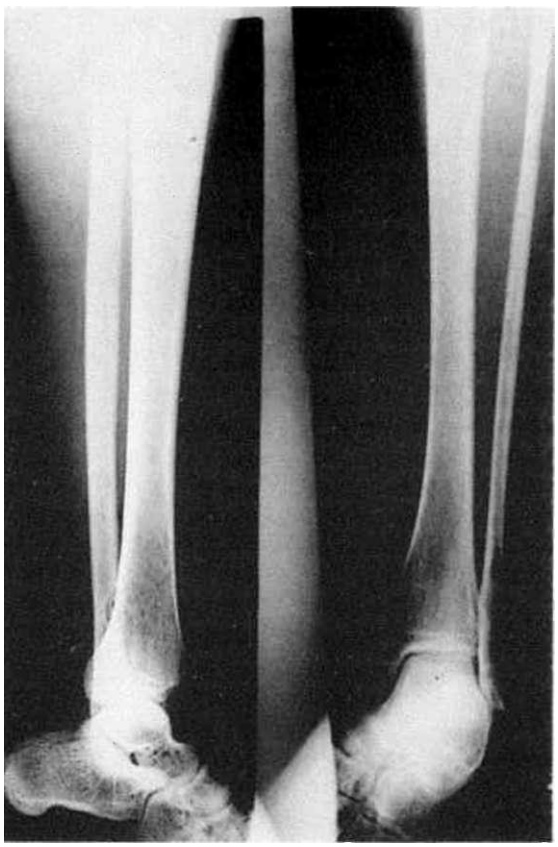

Figure 1b. Subperiostal cyst at right fibula distal part.

Recklinghausen's disease (1). It is well described in the cutaneous, osseous and central nervous systems. Involvement of thoracic blood vessels which may result in spontaneous hemothorax during pregnancy and gestation, may accelerate the disease.

This disease which was first described by German pathologist Friedrich von Recklinghausen in 1882, occurs with a frequency of approximately one in 3000 live births (2).

CASE REPORT

A 19-year-old girl applied to our Reproductive Endocrinology Clinic with a history of breast underdevelopment and left vulvar mass. She had had menarche when she was 13 years old and had menses rarely (at 3-6 months intervals) since then. In her history, the external genitalia was normal at birth but, the mass developed in a year's time, There was no history of any drug intake during the pregnancy of her mother. There was no family history of neurofibromatosis.

On examination, there was a 4x3x3 cm large left vulvar semisolid mass and there were multiple disparate cafe au lait spots all over her body. Height, weight and blood pressure were normal for age.

Breast development was at level II according to Tanner staging. She had scarse pubic hair and no axillary hair at all. Her vaginal introitus was normal, clitoris was normal. Routine hemograms, serology tests were normal. Karyotype was 46, XX.

Ultrasonography of the abdomen was normal, pelvic ultrasonography revealed out a uterus of 46x34x36, bilateral polycystic ovaries of normal size. At IVP, double ureter and double pelves were revealed out.

Because of the multiple café au lait spots all over her body, as she was thought to have neurofibromatosis, her whole body x-rays were done. Those revealed out that there was a cortical cyst at right femur distal lateral part, a subperiosteal cyst at right fibula distal part and an osteophyte at left tibia proximal part, coccyx was deviated to right and internally (Figure 1a, 1b). X-ray of the head bones revealed no deformity. Posteroanterior thorax x-ray was normal, involving the ribs too,

Cranial tomography was normal without any tumor effect.

She had androgens within normal limits where as estradiol and gonadotropins were within hypogonadotropic range at the moment she applied to our unit and she was amenorrheic for 3 months then (Estradiol:

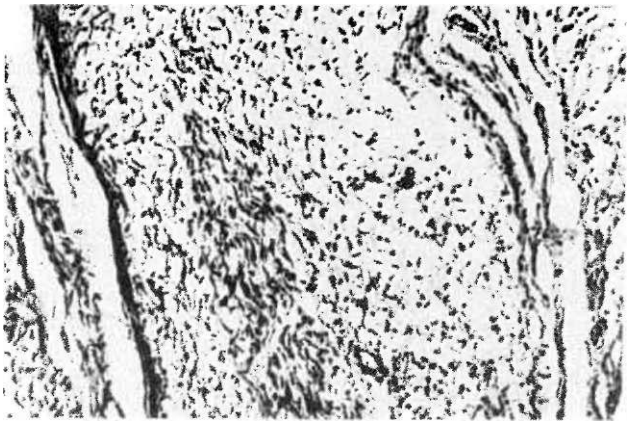

Figure 2. Neurofibroma

33 pg/dl, FSH: 4.3 IU/ml, LH: 4.9 IU/ml). Hormonal milieu other than these was normal.

The left vulvar mass was removed. Vulvar operation revealed that the mass was a well encapsulated tabulated mass that felt like a bag of warms. The mass was resected completely with minimal bleeding. Obvious enlargement and tortuosity of the nerve bundles were noted. The histological appearance was consistent with plexiform neurofibroma which is characterized by a disordely pattern of fibers and combined proliferation of all elements of a peripheral nerve (Figure 2).

Convalescence was uneventful. At-follow-up, 5 weeks postoperatively the results was statisfactory.

She is under hormone replacement therapy for breast development and regular menses. She is under control in case any other problem involving any other organ systems may occur in the mean time.

DISCUSSION

There is wide variation in the reported incidence of genital involvement with neurofibromatosis. Adkins and Ravitch found genital tumors in 3 of 85 pediatric patients with this disease seen over a 24 year period (3). Schreiber, on the other hand, reported ten instances of vulvar involvement among 53 females of all ages with the disease. This discrepancy may reflect the development of fibrous masses later in life, after the "pretumorous" phase characteristic of childhood (4).

Neurofibromatosis can be variable in its expression and Riccardi has described eight variants of the disease (Table 1) (5). Ninety percent of patients develop generalized expression to a greater or lesser extent. Over 20 cases of vulvar neurofibromatosis have been reported and most of these were in patients with type I neurofibromatosis (6). In fact vulvar involvement in this type of the disease is probably not rare, however genital involvement more frequently exists as clitoral occurance rather than vulvar involvement which is the case in our patient.

Lesions that have involved the clitoris have been confused with pseudohermaphroditism; According to the literature review of Messina and Strauss, 12 cases of vulvar involvement associated with the clitoris were reported (7).

Fodor has described a case of vulvar elephantiasis in a 11-year-old girl (8) and two cases of giant neurofibromas of the labia were reported from South Africa (9). Our case also involved labium majus without involving the clitoris.

There is a high rate of spontaneous mutation, which explains the lack of family history in about 50% of the reported pediatric cases. Our case also lacked such a family history.

Café au lait spots, one of the important diagnostic criteria of this disease, are present in almost all patients with neurofibromatosis. The skin is involved most frequently by neurofibroma. Involvement of genitourinary tract is rare but when it does occur bladder is affected most often (10). Here in our case only duplication of pelvis and ureters were detected.

Our patient has skeletal cysts which were very common for neurofibromatosis, like-erosions, cysts, overgrowths, pseudoarthroses, hemihypertrophy and bowing too. Nevertheless deforming scoliosis and skull and facial bone deformities are the most frequent and serious skeletal defects, those of which couldn't be found out in our case.

Precocius or retailed sexual development have long been recognized as complications of neurofibromatosis. However, abnormalities of sexual maturation are infrequent and are usually related to secondary involvement of target organs. Infertility may occur but usually they don't have difficulties to get pregnant. Mostly these patients appear with signs of precocious puberty rather than hypogonadotropism which is the case in our patient. Our case is oligomenorrheic therefore under hormone replacement to prevnet the risks of low estrogen exposure.

The incidence of malignant degeneration in neurofibromas ranges from 5-16%. The incidence of malignant

Table 1. Riccardi's classification of neurofibromatosis

Type	Features
I.Von Recklinghausen's disease	Multiple cafe-au-lait spots; Lisch nodules; neurofibromata
11.Acoustic	Few café au lait spots and neuro-fibromata; bilateral acoustic tumours
III.Mixed	Intermediate between first two types
IVVariant	Café au lait spots or tumours in one unilateral segment
VI.Cafe-au-lait spots	Cafe-au lait spots only
VII.Late onset	Onset of disease after age 30
VI11.Not otherwise specified	Cases not characteristic of any other category

degeneration in cases of generalized neurofibromatosis has been reported to be as high as 25 percent and it has been noted to increase with age (11).

In this case, genital involvement besides cutaneous involvement noticed as the neurofibrous tumors may prevent compromise of adjacent structures and possess malignant potential. We excised labial tumor, but even when the tumours pose only a cosmetics threat, there is little reason to ignore their presence.

Our patient is under periodic control for this reason and for hormone replacement therapy.

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