Clitoromegaly in type 2 neurofibromatosis: A case report and review of the literature

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Summary

Objective: Genitourinary neurofibromatosis (NF) is a rare disorder and clitoral involvement has been reported infrequently. In the English literature there are only 26 reported cases with clitoral involvement in NF.

Case: A 28-year-old female with clitoral enlargement, previously diagnosed with NF 2, was successfully treated by removal of the clitoral mass that increased in size during the previous two years. Clitoroplasty was performed while preserving the glans of clitoris. Histopathologic examination revealed plexiform neurofibroma.

Conclusion: To the best of our knowledge the patient is the 27th reported clitoromegaly case with NF, but the first case reported with NF 2 or central NF in the English literature.

Key words: Clitoromegaly; Clitoroplasty; Hypertrophy of clitoris; Neurofibromatosis 2.

Introduction

Neurofibromatosis (NF) is a genetic disorder affecting the skin and the nervous system, which was first described by von Recklinghausen in 1882 [1]. The gynecological problems of NF are not well documented. The clinical suspicion of NF would in most cases improve patient care and prevent undue procedures [2]. Genitourinary NF is rare and clitoral involvement in NF has been reported infrequently [3]. However, we were not able to find a case that reported NF 2 with clitoromegaly in the English literature.

Case

A 28-year-old white female, 162 cm in height and 44 kg in weight, presented with enlargement of the clitoris. She noticed that the mass in her early adulthood had increased in size especially during the previous two years. She was anxious about this cosmetically disfiguring lesion and the nature of the disease. She had been married for seven years and infertile for five years but was not examined for this reason. Her menstrual periods were regular. She had been diagnosed as NF 2 ten years before and had been operated on three times; first for a spinal tumor eight years prior, second for an acoustic neuroma with a translabyrinthine approach three years previously and third for parasagittal meningiomas with radiosurgery two years before. There was no family history of NF nor were we able to obtain any information about her mother's pregnancy history.

On physical examination, there was no symptom or sign that indicated endocrinopathy. She had unilateral sensorineural hearing loss and facial palsy on the left side which developed after her second operation. She also complained of a painful mass, 4 cm in diameter, located subcutaneously on the thoracic wall.

On pelvic examination, the clitoris measured 5 x 4 x 2.5 cm in size (Figure 1). It was firm but not painful on palpation. Other pelvic structures were within normal limits. There was no

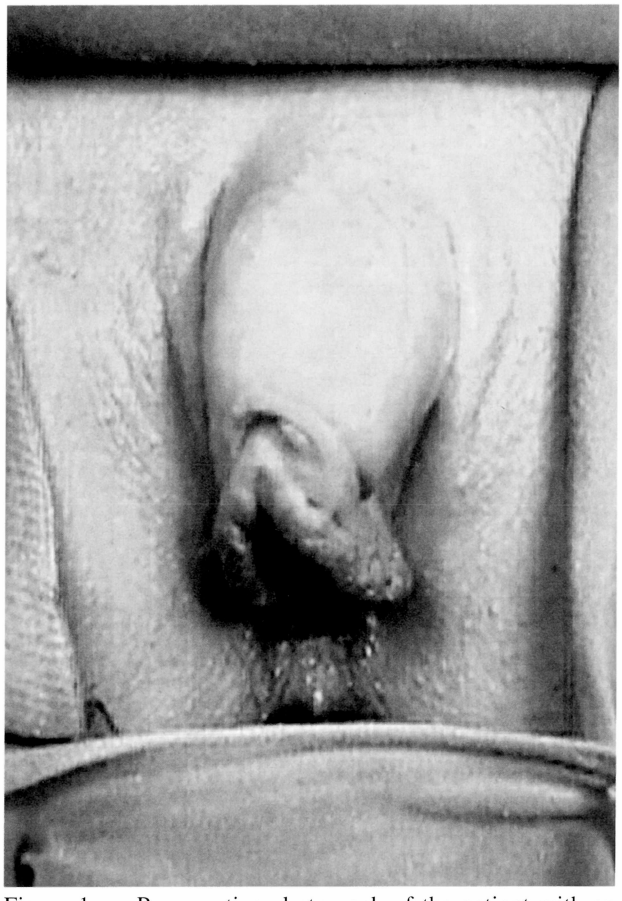

Figure 1. — Preoperative photograph of the patient with an enlarged clitoris.

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sign of androgen excess. A few small subcutaneously located tumors were noticed on her trunk but there were no café-au-lait spots nor Lisch nodules.

Routine hematologic and serum values were within normal limits. Cerebral magnetic resonance (MR) imaging and computed tomography (CT) demonstrated bilateral acuoustic neuromas, (two meningiomas located bilaterally in the occipital convexity and one in the right cavernous sinus, (Figure 2), multiple schwannomas (located in the cervical and lumbar spinal cord), and an ependymoma at the Th-12 level (Figure 3). Her lordotic angle was increased and the posterior components of the cervical vertebrae were defective. The intra-abdominal and pelvic organs were normal.

During the operation, a vertical skin incision performed on the dorsum of the clitoris revealed a semisolid mass. It was not possible to identify Buck's fascia because of the enlarging and infiltrating mass. The tumor was easily detached from the surrounding tissues while preserving the glans of clitoris (Figure 4). Bleeding occurred mostly from the proximal part of the tumor as expected; however, hemostasis was easily accomplished. After the completion of hemostasis, the cavity and the skin were closed with primary sutures with 3-0 polyglactin. The mass on the thoracic wall was also resected. On the second postoperative day, oedema developed which resolved on the sixth day. The patient was discharged on the seventh day. She was emotionally stable and satisfied with her appearance at the follow-up examination one month after the operation (Figure 5).

Histopathologic examination revealed a plexiform neurofibroma encapsulated with fibrous tissue, with the tumor cells S 100 (+) and actin and desmin (–) dyed immunhistochemically (Figure 6). The thoracic wall mass was also diagnosed as a plexiform neurofibroma.

Discussion

The term neurofibroma denotes two separate disease entities, NF 1 or von Recklinghausen's disease and NF 2, each caused by a different gene [4]. Clinical manifestations and diagnostic criteria are different for each type of NF [5]. NF 1 is the most prevalent type with an incidence of one in 3,000 [4] or 4,000 [5] and is caused by a mutation of the 60 exon NF 1 gene on chromosome 17q [4]. NF 1 is diagnosed if any two of the following signs are present: (1) six or more café-au-lait macules over 5 mm in the greatest diameter in prepubertal individuals and over 15 mm in the greatest diameter in postpubertal individuals, (2) axillary or inguinal freckling, (3) two or more iris Lisch nodules, (4) two or more neurofibromas or one plexiform neurofibroma, (5) a distinctive osseous lesion, (6) optic gliomas, (7) a first-degree relative with NF 1 whose diagnosis was based on the aforementioned criteria [5].

NF 2 may be diagnosed when one of the following is present: (1) bilateral eighth nerve masses consistent with acoustic neuromas as demonstrated by CT scanning or MRI, (2) a parent, sibling or child with NF 2 and either an unilateral eighth nerve mass or any two of the following: neurofibroma, meningioma, glioma, schwannoma, or

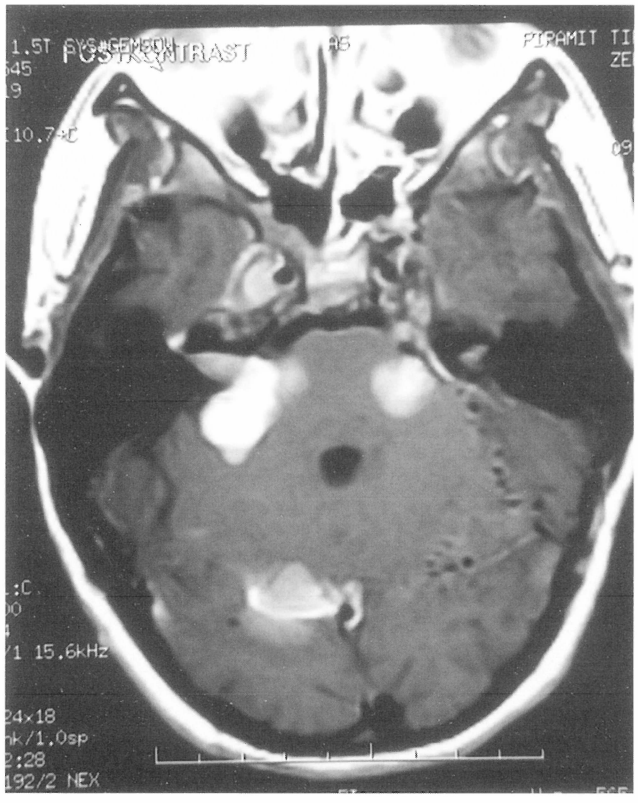
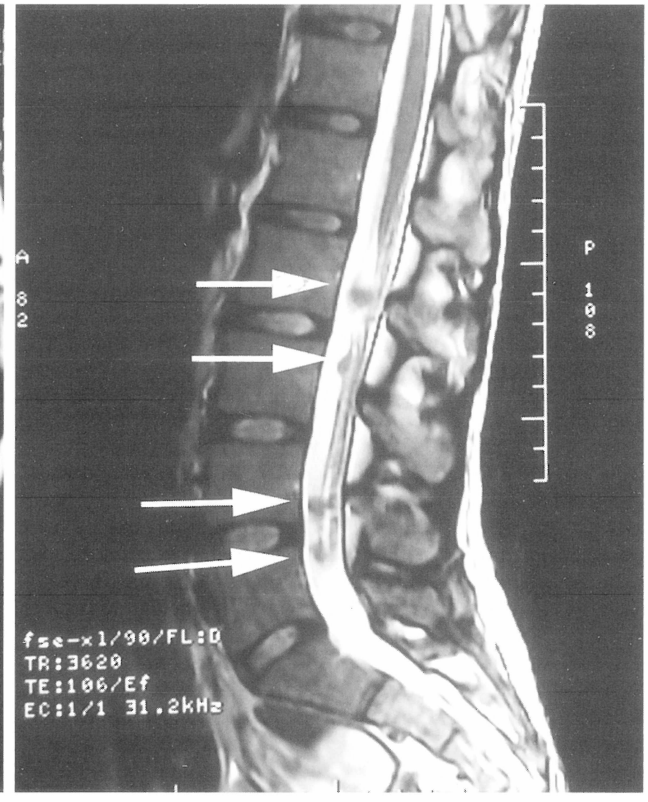


Fig. 2



Fig

Figure 2. — Cranial MR imaging disclosing a bilateral acoustic neuroma in the pontocerebellar angle and one meningioma in the occipital region.

Figure 3. — Spinal MR imaging showing multiple intraspinal masses diagnosed as schwannoma.

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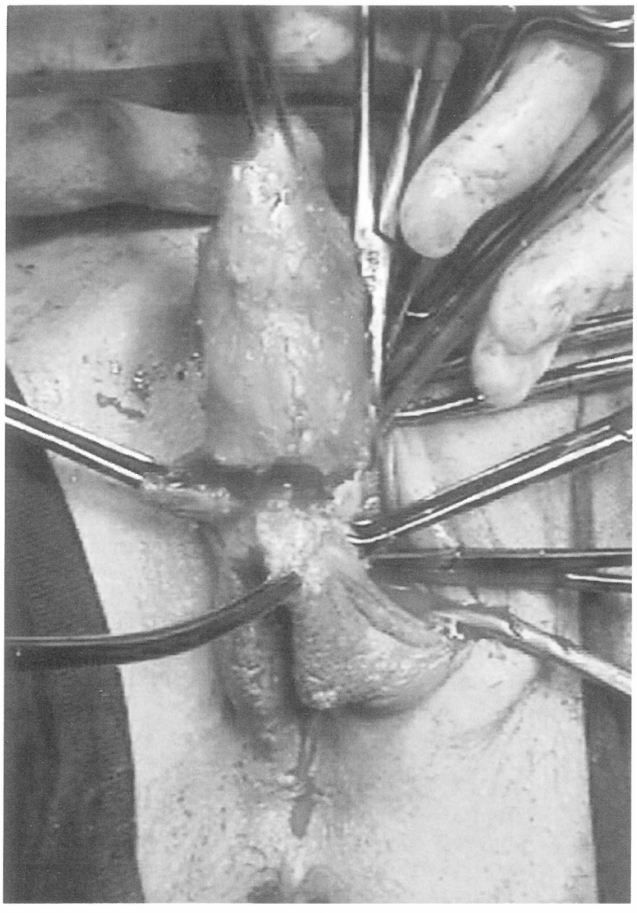

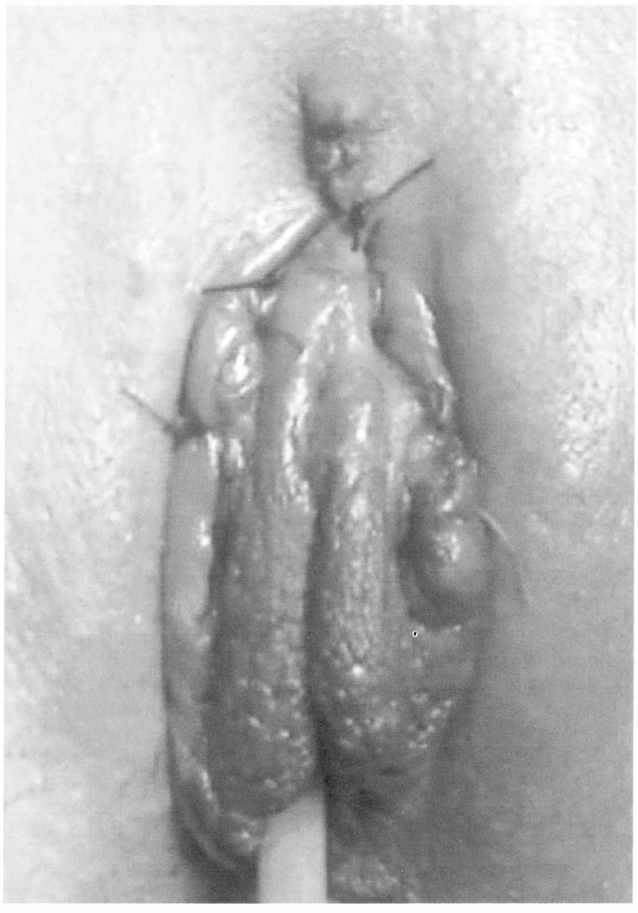

Fig. 5

Figure 4. — Intraoperative photograph showing the removal of the tumor mass in the clitoris.
Figure 5. — Postoperative appearance of the surgical area with preservation of the glans.

juvenile posterior subcapsular lenticular opacities [6].

Patients with NF 2 have few cutaneous lesions but often have multiple types of tumors of the central nervous system (CNS), so this type of NF is also named as central NF [1, 7]. Symptoms of NF 2 typically develop in adolescence or early adulthood, although children can be affected. NF 2 occurs in only one out of 50,000 people [1, 4]. NF 2 is caused by a mutation of the NF 2 gene on chromosome 22 which suppresses tumor function and its dysfunction accounts for the common occurrence of CNS tumors in patients with NF [1, 4, 7-9]. Malignant transformations rarely occur in neurofibromas [10].

Clitoromegaly can be seen as congenital or acquired so in any age. The majority of clitoromegaly cases related with NF are congenital. The differential diagnosis of ambiguous genitalia should include clitoromegaly due to NF [3]. A patient was reported who had localized enlargement of the prepuce only, with no evidence of neurofibromatous infiltration [12].

In the etiology of acquired clitoral hypertrophy, the following three are the most frequent: (1) endocrinopathies including virilizing tumors of the ovaries or adrenals, (2) NF (of both clitoral subcutis and corpora cavernosa), and (3) pseudohypertrophy of the clitoris [12]. The first step in correcting acquired clitoral enlargement must be to determine and stop the cause of the hypertrophy, followed by a period of simple observation but surgery might be inevitable [12]. Clitoromegaly in adulthood may not be very complex for evaluation but it may be a problem and important in childhood. Unfortunately, it may sometimes be misdiagnosed [13].

Since the first report of clitoral neurofibroma in 1960 by Haddad and Jones [14], there have been 27 case reports of the lesion in the English literature, including our case (Table 1) [2, 3, 13-33] and also four case reports in other languages [3] that we have not reviewed. The range of age of these cases is 11 days to 28 years at the time of diagnosis. Of the 27 case reports, the first 14 were reported before 1987, the time at which the current NF typing was accepted. Although lack of some knowledge to definitely establish the type of NF of these reports, neither the previous 14 nor the 12 cases reported after 1987 met the diagnostic criteria of NF 2. The present case met the criteria of NF 2 and it is the first case of NF 2 with clitoromegaly.

Surgical treatment of ambiguous genitalia can be classified as follows: (1) exploratory surgery for diagnostic

Table 1. — *Clitoral involvement in cases of neurofibromatosis.*

Reference	Age	Clitoral histology	Cls	Family history	Probable type of NF	Associated involvement	G-U Treatment
Haddad and Jones, 1960 [14]	9 y	NF	+	+	1	None	Clitorectomy
McKeown and Frazer, 1961 [15]	11 d	NF	+	NS	1	None	None
Schreiber, 1963 [16]	11 m	NS	+	+	1	None	None
Van Buskirk *et al.*, 1964 [17]	20 m	Plexiform NF	+	–	1	Bladder and perivesicular	Partial clitorectomy
Kenny *et al.*, 1966 [18]	15 y	NF	+	+	1	Labia majora	Clitorectomy
Knudson and Amromin, 1966 [19]	7 y	NS	+	–	1	None	NS
Labardini *et al.*, 1968 [20]	12 y	NF	+	+	1	Labia majora, bladder and perivesicular	Clitorectomy
Messina and Strauss, 1976 [21]	17 y	Plexiform NF	+	NS	1	Bladder, perivesicular, perivaginal and retroperitoneal	NS
Franceschini *et al.*, 1978 [22]	7 y	NF	+	NS	1	Labia majora, bladder	NS
Greer and Pederson, 1981 [23]	4 y	NF	+	NS	1	Labia majora	Clitorectomy
Schepel and Tolhurst, 1981 [24]	6 y	NF	+	+	1	Labia majora	Partial clitorectomy
Craven and Bresnahan, 1983 [25]	12 y	NF	+	+	1	None	Partial clitorectomy
Ravikumar and Lakshmanan, 1983 [26]	3 y	NF	+	–	1	None	Partial clitorectomy
Rink and Mitchell, 1983 [27]	5 y	Plexiform NF	+	+	1	Bladder, perivesicular, ureters and vaginal	Partial clitorectomy
Haraoka *et al.*, 1988 [28]	10 y	NF	+	–	1	None	Partial clitorectomy
Kaneti *et al.*, 1988 [29]	8 y	Plexiform NF	+	+	1	None	Partial clitorectomy
Thomas *et al.*, 1989 [30]	14 m	Malignant schwannoma	+	+	1	None	Radical clitorectomy
Nogita *et al.*, 1990 [31]	11 y	NF	+	–	1	Labia majora	Partial clitorectomy
Griebel *et al.*, 1991 [11]	25 m	No NF	+	+	1	None	Partial clitorectomy
Nishimura *et al.*, 1991 [13]	5 y	Plexiform NF	–	–	1	None	Clitorectomy
Nonomura *et al.*, 1992 [32]	6 y	Plexiform NF	NS	+	1	None	NS
Kearse and Ritchey, 1993 [33]	8 y	Plexiform NF	+	+	1	None	Partial clitorectomy
Sutphen *et al.*, 1995 [3]	3 y	NF	+	+	1	None	Partial clitorectomy
	22 m	No NF	+	+	1	None	Partial clitorectomy
	4 y	No biopsy	+	+	1	None	None
	6 m	No biopsy	+	+	1	Mons pubis	None
Present case	28 y	Plexiform NF	-	-	2	None	Tumor resection

NS = not stated; Cls = Café-au-lait spots; G-U = genitourinary; y = year(s); m = month(s); d = days.

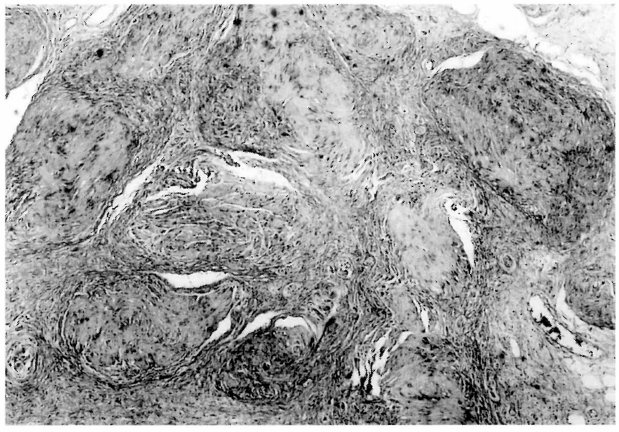

Figure 6. — Histologic appearance of plexiform neurofibroma of the clitoris. H & E, reduced from x 100.

purposes, (2) excisional surgery for diagnostic purposes, and (3) reconstructive surgery [34]. All of them are also suitable reasons why surgical intervention was necessary for our patient. The source of knowledge about clitoral surgery generally comes from some primitive tribe interventions and intersex cases. The clitoral enlargement may affect the patient emotionally. Preservation of ventral and dorsal vascular pedicles at clitoroplasty has had satisfactory results in sexually mature women. Optimal sexual function after surgical correction of clitoral hypertrophy requires an adequate postoperative innervation and vascular supply to the glans clitoris. Several clitoroplasty methods have been reported, but few describe the preservation of dorsal and ventral neurovascular bundles in sexually mature women [35]. Biopsy of such lesions appears to be justified only when malignancy is suspected [3]. In the present case no signs of malignancy were observed preoperatively and therefore diagnostic biopsy was not attempted. Clitoroplasty with sparing of the neurovascular bundle and glans is the preferred method in the management of an enlarged clitoris, as in our case [11].

In summary, NF must be considered to avoid unnecessary interventions in the differential diagnosis of ambiguous genitalia. Clitoromegaly may also be a manifestation of both types of NF, especially when encountered in childhood and these patients must be evaluated for NF. We conclude that resection with preservation of the clitoris is the preferred surgical approach in patients with clitoromegaly due to NF with satisfactory results.

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