Abnormal Presentation of Neurofibromatosis
Review of the Literature

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Abstract:
Multiple Neurofibromatosis (NF) is a disease of great interest because of the familial nature of the disease, the complexity of its morphology, the progressive character of its course and the numerous complications that may develop during its evolution. The authors present a late presentation of a genital NF type 1 affecting the penis and the right lower limb of a young adult.

Key words: Neurofibromatosis, Penis

Case Report:
A 20-year-old expatriate male was referred with impotence and unusual painless swelling of the genitalia and the right thigh. The histories of the beginning of the swelling, family history and the progress of the disease were not clear.

Examination revealed a large cone-shaped swelling involving the distal half of the penile shaft with the glans hidden when standing (Figure 1). Upon holding the penile skin distally the glans appeared surrounded by a whitish firm rubbery non-tender swelling, not tethered to the overlying skin, with no ulcerations showing through the mucosa as a lion mane (Figure 2). The right thigh had hairy pigmented skin over the postero-medial aspect, extending upward into the right gluteal region where it formed a large sagging hairy cutaneous lesion extending medially into the natal cleft (Figure 3).

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Figure 1: Standing anterior view; a cone-like swelling of the distal penile shaft, right thigh lesion and right inguinal freckles.

Figure 2: Lifting distal half of the penis; tumour surrounding the glans (as a lion head fur).

Figure 3: Posterior view, extent of the lesion into right thigh, perineum and gluteal region.
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The skin of the chest showed multiple 'cafe au lait' spots and there were similar freckles on the skin of the inguinal region. Ultrasound examination suggested hemangioma; MRI showed a large mass in the cutaneous and subcutaneous regions of the upper part of the right thigh, right-sided perineum, right ischiorectal fossa and penis, with findings suggestive of combined hemangioma and lymphangioma with no gross arterio-venous malformation. Penile Doppler ultrasound showed bilateral venous leaks.

The patient underwent excision biopsy of the penile swelling, measuring 14 x 4.5 x 2 cm, circumcision, and partial elliptical excision of the thigh skin lesion which measured 17 x 5 x 1 cm. Histopathology reported unexpectedly a diffuse neurofibroma with plexiform areas. His post-operative course was smooth and a penis of normal appearance was obtained (Figure 4).

Figure 4: Three months post-operative; a penis of normal appearance.

Discussion:

Neurofibromatosis (NF) is an autosomal dominant disorder of neural crest origin that affects all three germinal layers and therefore can involve any organ. It is not a single entity but a group of heterogeneous multisystemic neurocutaneous disorders involving both neuroectodermal and mesenchymal derivatives. Although eight subtypes have been proposed to date, Neurofibromas may affect any organ in the body. The National Institute of Health (NIH) Consensus Development Conference has defined only two distinct types. 7,18

Neurofibromatosis Type 1 (NF1), or Von Recklinghausen Disease, which affects 85% of patients.

Neurofibromatosis Type 2 (NF2), or bilateral acoustic neuromas/vestibular schwannomas, which affects 10% of patients.

NF1 (as in the case presented) is caused by decreased production of the protein neurofibromin, which has a putative tumour suppressor function. The NF1 gene has been localised to the long arm of chromosome 17; more than 250 mutations leading to protein truncation having been identified in affected individuals. Only one NF1 gene needs to be deleted or mutated to produce the condition but a more severe phenotype has been observed in a subset of patients with a complete gene deletion. 11 NF1 is one of the most common autosomal dominant genetic disorders with an incidence of one case per 3,000-4,000 people, half the cases being caused by new mutations. The mutation rate in the NF1 gene (1/10,000 population) is among the highest known for any human gene but the cause is unknown. In familial cases expressivity of the disorder is variable but the penetrance is 100%. 19

Discrete cutaneous and subcutaneous neurofibromas may develop at any time of life but they occur infrequently before puberty. Additional cutaneous and subcutaneous neurofibromas continue to develop throughout life although the rate of appearance may vary greatly from year to year. 19

NIH criteria for the diagnosis of NF1 are met in an individual if two or more of the following signs 11 (based on physical and radiological findings) are found:

- Six or more 'cafe au lait' macules larger than 5 mm in the greatest diameter in prepubertal children and larger than 1.5 cm in post-pubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Multiple freckles (Crowe sign) in the axillary or inguinal region
- A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudoarthrosis.
- Optic glioma
- Two or more iris hematomas (Lisch nodules) seen on slit-lamp or biomicroscopy examination
- A first-degree relative (parent, sibling, offspring) with NF1.

Plexiform NFs are peripheral nerve tumours (composed of Schwann cells, fibroblasts and connective tissue). An enlarging lesion or, if associated with pain, a biopsy is essential for diagnosis. Most spinal nerve root NFs remain asymptomatic and do not need to be removed. 19

Genito-urinary neurofibromas in females are rare and are even more infrequent in males. The most frequent presenting sign in females is clitoromegaly with pseudopenis, and an enlarged penis is the common sign in males, usually associated with involvement of other areas such as the lower abdomen, perineum, gluteal area and thigh. 1,2,3,5,6 An isolated single scrotal mass has been reported in a 77-year-old man. 4 Although impotence in such patients has not been studied much due to rarity, some have mentioned erectile dysfunction due to arterial steal. 20 In our case it was due to a bilateral venous leak detected by penile Doppler ultrasound.
References