Abstract

Neurofibromatosis type 1 (NF-1), formerly known as von Recklinghausen disease, is an autosomal dominant multisystem disorder characterized by skin manifestations, skeletal abnormalities and nervous system involvement. A typical case with a prevalence of 1: 2500 to 1: 3500 people, this case report can also be expected to provide additional insight. We report a case of a 14-year-old girl with complaints of skin and soft lumps in almost all body parts for the past eight years—the appearance of multiple lenticular to plaque size café-au-lait macules since the age of one. In the gluteus region, plexiform neurofibroma is found with indistinct borders. The histopathological result supports the diagnosis of neurofibromatosis. The patient was also consulted by an ophthalmologist and found Lisch’s nodules in the left eye. Lumbosacral AP/ lateral radiography showed dextro-convex lumbar scoliosis. Based on the National Institutes of Health conference in 1987, NF-1 can be diagnosed when two or more out of seven diagnostic criteria are met. The patient was diagnosed as NF-1 and received surgical excision therapy.

Keywords: Neurofibroma, Neurofibromatosis type 1, von Recklinghausen

Introduction

Neurofibromatosis type 1 (NF-1), also known as Von Recklinghausen’s disease, is an autosomal dominant multisystem disorder characterized by skin manifestations, skeletal organ abnormalities and nervous system. The prevalence ranges from 1: 2500 to 1: 3500 individuals in all ethnicities, races, and sexes. [1] The manifestation of NF-1 results from the mutation of the NF-1 gene located on chromosome 17q11.2, which encodes the neurofibromin protein that functions as a tumour suppressor. [2] The National Institutes of Health conference in 1987 appointed seven diagnostic criteria based on clinical studies of patients with NF-1 in which the diagnosis can be established when two or more of those criteria are met. [3] Neurofibromas are benign tumours originating from nerve tissue. Clinically this tumour can be assessed by examining the ‘button hole’ sign, where the tumour will enter its panniculus upon light pressure and return to its original position when released. [4] The two preferred management approaches of NF-1 are surgical therapy in progressive lesions and genetic counselling. Dermal neurofibromas can be removed by excision, CO2 lasers, or electrodesiccation to improve appearance or comfort. [5]

Case report

History

A 13-year-old girl was referred to our department with generalized soft skin lumps for the past 8 years. The lumps were not painful nor itchy. The parents recalled the appearance of multiple hyperpigmented skin macules since the age of 1 year with various sizes. History of drug and food allergies were denied. She had been previously treated at the primary health center without any improvement.

Physical Examination

Dermatological examination showed multiple skin-coloured neurofibromas and hundreds of lenticular to plaque-sized hy-
perpigmented skin macules on the chest and back, multiple café-au-lait macules with diameter >1.5 cm (Figure 1A,1B), and axillary freckling (Figure 1C,1D). In the gluteal region, plexiform neurofibroma with indistinct borders was found (Figure 2).

**Laboratory, Imaging Studies and Histologic Findings**

The standard laboratory tests values were in normal range. Lumbosacral anterior-posterior/lateral radiography showed dextroconvex lumbar scoliosis (Figure 3). Histopathological examination showed epidermis with intact basal layer, the proliferation of tumor cells in the dermal layer consisting of various types of cells; fibroblast cells, myofibroblast cells, and some Schwann cells (Figure 4). The histopathological result supported the diagnosis of neurofibromatosis.

**Ophthalmological Status**

The patient was consulted to the ophthalmology department, where multiple Lisch’s nodules on the iris in the left eye without any signs of visual involvement were found. (Figure 5)

**Diagnosis**

Based on the history, physical examination, and workup diagnostics, the patient was diagnosed with NF-1. The diagnosis NF-1 was made according to the presence of two or more diagnostic criteria published the National Institutes of Health conference in 1987 in this case, which was

a. Six or more café-au-lait spots measuring at least 5 mm before puberty or 15 mm after puberty

b. Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma

c. Axillary or inguinal freckling

d. Two or more Lisch’s nodules

e. Scoliosis

**Therapy**

Surgical excision of some progressive neurofibroma to prevent local irritation was performed and showed a good cosmetic result.

**Discussion**

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen’s disease, is an autosomal dominant multisystem disorder characterized by the findings of neurofibromas, café au lait macules, plexiform neurofibromas, Lisch’s nodules and scoliosis.

[1]

In our case, there was no family history with a similar complaint. Although NF-1 is considered an inherited disease, only 50% of people have one or more family member affected by NF-1. As such, 50% of patients will be the first person in their family with NF-1 because of the high spontaneous mutation rate of NF-1.[6]

Dermatological examination found soft and painless skin-coloured neurofibromas. Like most feature in NF-1, the presence of neurofibroma is age-dependent. Although neurofibromas tend to increase with age, the presence of plexiform neurofibromas may have already manifested at birth and are most active.
Clinical diagnostic criteria for neurofibromatosis-1 (NF1)

Patients have two or more of the following symptoms:

1. Six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals, and larger than 15 mm in greatest diameter in postpubertal individuals

2. Two or more neurofibromas of any type or one plexiform neurofibroma

3. Freckling in the axillary or inguinal regions

4. Optic glioma

5. Two or more iris Lisch’s nodules

6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis

7. A first degree relative (parent, sibling, or offspring) with neurofibromatosis type 1 by the above criteria

Figure 3: Lumbosacral AP/ lateral radiography of dextroconvex lumbar scoliosis.

Figure 4: (A) epidermis with intact basal layer (x40) (B) dermis layer consisting of various types of cells; fibroblast cells, myofibroblast cells, and some Schwann cells (x100).

Figure 5: Iris Lisch’s nodule.
during the first decade of life. [7] Neurofibroma is a stemmed or dome-shaped skin-coloured or brownish pink soft tumor that clinically resembles a hernia. [8,9] The buttonhole sign is crucial in distinguishing neurofibroma from intradermal nevi or dermatofibromas, reported in our case. [4,10] There are four subtypes of neurofibromas: cutaneous, subcutaneous, nodular or diffuse plexiform and spinal. [6] Plexiform neurofibroma occurs in 30-50% cases of NF-1; it comprises beads or spindles form of peripheral nerve neurofibroma that appears on the skin above the subcutaneous nerve, hence sometimes causing pain. These tumours are soft, loose, and irregular with unclear border and characterized by hyperpigmentation. [11] In our case, an asymptomatic plexiform neurofibroma with an indistinct border was found on the gluteus. The consistency is a little hard, described as a “bag of worms” sensation upon palpation of the multilobulated lesions. [12] There were generalized café-au-lait macules and freckles in the axilla were known as Crowe’s sign in our case. Hyperpigmented macules and freckles with varying sizes from lenticular to nummular were found on the inguinal of this patient, and the lesions were not pruritic nor painful. Café-au-lait macules are present in up to 95% of newborns with NF-1, and the spots tend to expand with age. [8]

Extracutaneous features are also commonly found in NF-1. Ophthalmological examination showed multiple of Lisch’s nodules on the left eye with no visual impairment. Lisch’s nodules are benign melanocytic hamartomas of the iris. They vary in size and have a smooth, dome-shaped configuration. [13] Unilateral Lisch’s nodules are rare; they are mostly reported in cases of segmental neurofibromatosis and found in association with other pigmentary change or neurofibromatosis. Genetic factor has been associated with unilateral Lisch’s nodules. Huson et al. reported that Lisch’s nodules were present in 95% of their patient (61/64) and were bilateral in 93% (57/61). It was typically found in children aged 5–10 years, and almost all adults with NF-1 have Lisch’s nodules. [12] There was a highly significant correlation between age and the number of nodules per eye. Viola et al. reported that Lisch’s nodules were detected by slit-lamp examination in 68 (72%) of 95 adult NF-1 subjects and nine (43%) of 21 pediatric NF-1 subjects. [14]

Physical examination showed that the vertebrae were not straight, and AP/ Lateral lumbosacral radiography revealed dextro-convex lumbar scoliosis. NF-1 can cause bone abnormalities, including osteopenia, scoliosis, sphenoid dysplasia, congenital tibial dysplasia and pseudarthrosis. [15,16] Scoliosis is the most common musculoskeletal manifestation of NF-1. It may vary in severity from mild and nonprogressive to severe curvatures. Erosion or infiltration of the bone by localized neurofibromas was suggested as one of the main causes of scoliosis. [17]

According to the 1987 National Institutes of Health conference, seven diagnostic criteria were appointed based on clinical studies, where NF-1 can be confirmed when two or more criteria are met. (Table 1) The histopathological results of our case showed epidermis with an intact basal layer; meanwhile, in the dermis, the proliferation of tumour cells consisting of various cell types such as fibroblasts, myofibroblasts, and some Schwann cells was found. Histopathologically, NF-1 is a collection of nerve fibres that are encapsulated and well-circumscribed with spindle cells in the dermis. There are a pale cytoplasm and an elongated core. These spindle cells represent a mixture of fibroblasts, Schwann cells and perineural cells arranged in collagen stroma with varying and scattered numbers of mucin cells and mast cells. [12,18]

The two main management of NF-1 is surgical therapy in progressive lesions and genetic counselling. Discrete cutaneous neurofibromas can be removed surgically to improve cosmesis. Deeper neurofibromas may require surgical removal if they invade the vital structure. [3] Dermal neurofibromas removal can also be performed using CO2 lasers or electrodesiccation to improve appearance or comfort. [5] Surgery for benign plexiform neurofibroma is often very difficult since the invasion of the tumour to the surrounding structures and nerves are often accompanied by vascular involvement. [19] Efforts to remove the café-au-lait macule with laser therapy such as Q-switched ruby (694 nm) or YAG (2.940 nm) have yielded very diverse results. [3]


