CASE REPORT

An Unusual Presentation of Neurotized Congenital Giant Melanocytic Nevus and Type 1 Neurofibromatosis: A Diagnostic Challenge

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ABSTRACT

Among the three subtypes of neurofibromatosis are type 1 and 2 neurofibromatosis and schwannomatosis, von Recklinghausen disease also known as type 1 neurofibromatosis has an autosomal dominant inheritance. It is the commonest form as and presents with numerous cafй-au-lait macules and neurofibromas. Giant congenital melanocytic nevus (CGMN) on the other hand is characterized by a melanocytic proliferation that present at birth. CGMN develops due to a defective embryonic pigment cell (melanocyte) precursors development and are often present at birth. Giant congenital melanocytic nevus (CGMN) and type 1 neurofibromatosis may occur together rarely. Clinicians should be aware of the rare presentation of both CGMN and type 1 neurofibromatosis in a patient.

Keywords: Neurotized Congenital Giant Melanocytic Nevus, Neurofibromatosis Type 1

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INTRODUCTION

Type 1 neurofibromatosis is a genetic condition with an incidence of around 1 in 2600-3000 individuals (1). Genomic studies showed that the abnormal NF1 gene is situated on the chromosome 17q11.2 (1). On the other hand, a congenital melanocytic naevus is a proliferation of melanocytes that are present at birth or soon after birth. NRAS mutations has been the most frequent reported. There are known somatic mutations among the intracellular proteins of microtubule associated protein signal transduction pathway that leads to the development of CGMN (2). Often, they present at birth and grow proportionally with a child. A literature search had been performed and these two conditions had not been reported to occur simultaneously. We would like to report a rare presentation of a type 1 neurofibromatosis seen in a 15-years-old female who presented with neurofibroma like lesions over her face and discuss the possible differential diagnosis, clinical presentation, histopathological and immunohistochemistry features.

CASE REPORT

A 15-years-old female presented with a disfiguring left facial swelling which was present at birth and had grown remarkably larger during her puberty period (Fig. 1A & 1B). A three generational family history was negative of similar skin disorder or neurofibromatosis. During her pubertal period, the birth mark became more hyperpigmented and the swelling over her left neck extended to her left ear and surrounded her neck. The skin over the angle of her jaw down to upper chest was hyperpigmented, coarse with multiple folds of skin giving a 'bags of worms' texture on palpation. There were multiple cafй au lait spots seen over her trunk and limbs (Fig. 1C) with axillary (Fig. 1E) and inguinal freckling. There were Lisch nodules seen under slit lamp (Fig. 1D). Magnetic resonance imaging of the face and trunk was consistent with plexiform neurofibroma (Fig. 2A, 2B & 2C). Skin biopsy of her neck showed fairly symmetrical intradermal melanocytic lesion (Fig. 2D) which completely showing type C spindled-shaped nevus cells arranged in nests, solid sheets and dispersed cells singly (Fig. 2E) accompanied by occasional melanin pigment and melanophages (Fig. 2F). The latter was seen throughout the lesion. Mitosis was not seen. There were no proliferative nodule or regression seen. Junctional

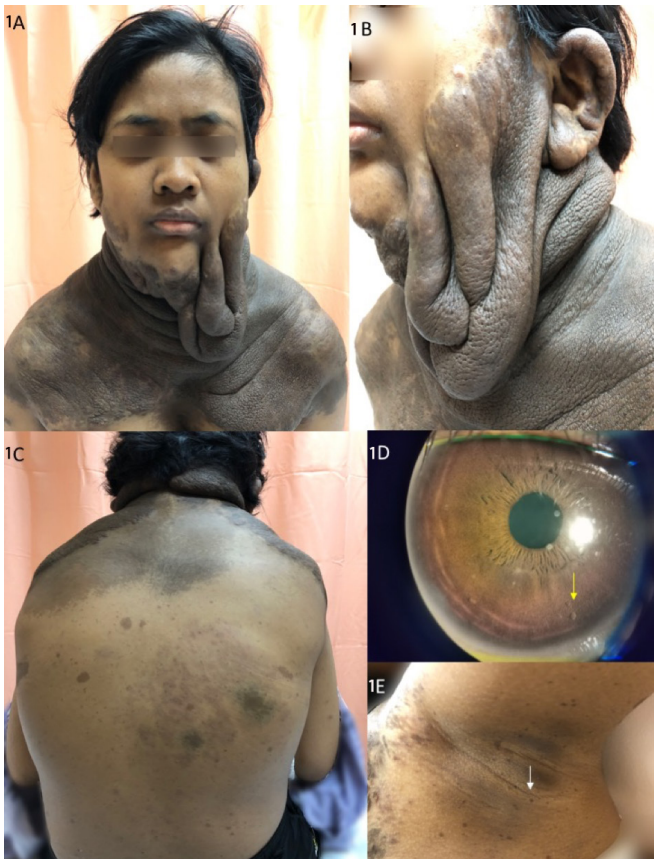

Figure 1: (A) Left facial plexiform neurofibroma. (B) Closer view of the left plexiform neurofibroma. (C) Multiple café-au-lait macules are seen on the back. (D) Lisch nodules (Yellow arrow). (E) Axillary freckling (White arrow).

activity was not a feature. Immunohistochemical studies showed the nevus cells were immunoreactive for S100 protein diffusely. Melan A showed focal weak positive but negative for HMB45 (Fig. 2G). Further stains with CD34, NSE and EMA are also negative. She was subsequently referred for cosmetic surgery.

DISCUSSION

There was a clinical concern of neurofibromatosis and CGMN mimicking each other in the case discussed above. Our differential diagnosis was CGMN and plexiform neurofibromatosis. Both melanocytes in melanocytic nevus and Schwann cells in neurofibromas originate from the neural crest stem cells (3). Hence, the distinction between heavily or completely neurotized melanocytic naevus and neurofibromatosis can be tough. According to literature search, CGMN occurred in around 5% of patients with type 1 neurofibromatosis (4). Our patient fulfils the NIH diagnostic criteria for neurofibromatosis where she had more than 6 cafй-au-lait macules measuring 6-10 mm in diameter, 8 neurofibromas, left facial plexiform neurofibroma, intertriginous freckling and Lisch nodules. She had a no history of first-degree relatives with type 1 neurofibromatosis. MRI confirmed the presence of left facial plexiform neurofibroma (Figure 2A, 2B & 2C). On the other hand, CGMN is classically described as melanocytic nevi occurring at birth or within the first few months of life and involved of at least 5% of body surface areas. The small nevi can become

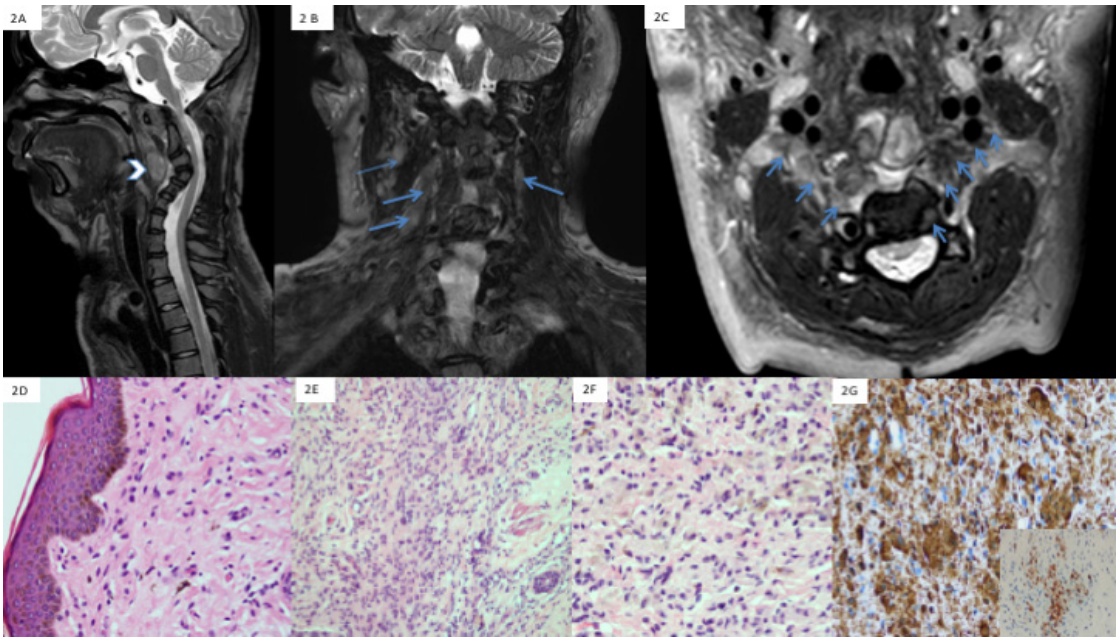

Figure 2: (A) (MRI image, sagittal T2W) shows increase lordosis with narrowing of the foramen magnum, causing impingement onto the cervico-medullary junction of the cord. Few prevertebral soft tissue lesions (arrowhead) seen anterior to the upper cervical vertebrae. (B) (MRI image, coronal STIR) and 2C (Axial T1-post contrast zoom in) show confluent of multiple nodular enhancing solid lesions (arrow) in both sides of the neck and prevertebral region. These lesions appear arising from the exiting nerve roots. (D) Intradermal lesion comprising of nevus in singly distribution. Note that there is no junctional activity (HE x 200). (E) Spindle shaped type C nevus cells arranged in solid sheet and irregular fascicles. Adnexal structure on the lower right is not invaded by the nevus cells (HE x 200). (F) The nevus cells exhibiting neurotised appearance. Melanophages are seen interspersed in between the nevus cells (HE x 400). (G) The nevus cells showing nuclear and cytoplasmic immunoreactivity for S-100 protein (x400). The inset illustrates the nevus cells are focally positive for Melan A (x 400).

more apparent during childhood. Frequently, there are numerous smaller generalized disseminated satellite nevi. The lesions often undergo age related changes in pigmentation. Histologically, both melanocytic nevus and neurofibroma are positive for S100 protein diffusely. Other melanocytic markers such as HMB45 and Melan A used to highlight the melanocyte can be negative in completely neurotized melanocytic nevus (4, 5). In the dermal melanocytes, neurotization takes place due to the alteration of oval shaped type A and B nevus cells into type C cells. The type A and B cells contain cytoplasmic melanin. On the other hand, the type C cells lack melanin and resemble neuroid structures of the dermis (3, 4). Her skin biopsy result was consistent with completely neurotized intradermal naevus which supports the rare presentation of both CGMN and plexiform neurofibromatosis in this patient.

CONCLUSION

Given the rarity of congenital giant melanocytic naevus and type 1 neurofibromatosis occurring together, clinicians should be aware of key features in differentiating both disorders (Table I). All CGMN child should be included on a long-term follow-up from birth due to the risk of development of malignant melanoma.

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Table I: Comparison of clinical and histologic features of CGMN and type 1 Neurofibromatosis

	CGMN	Type 1 Neurofibromatosis
Clinical features	Hyperpigmented lesion Satellite nevi	Hyperpigmented lesion Café-au-lait macules, Intertriginous freckling.
Palpation	Firm consistency	Bag of worms
Histopathology	Proliferation of junctional and intradermal melanocytic cells arranged in islands and nesting patterns with maturation with type A to type B and C nevus cells. Pigmentation is common finding.	Proliferation of all elements of peripheral nerves (Schwann cells, stromal mucosubstances, mast cells, axons, fibroblasts and collagen). Proliferation of abnormal nerve segments or plexiform foci. Pigmented (melanotic) variant is well recognized.
Immunohistochemistry	PositiveforS100,HMB45,MelanA,SOX10andMiTF. Type C / spindle shaped nevus cells: Loss of HMB45 and Melan A positivity (indicate maturation)[8].	Positive for S100, NSE, CD 57 (Leu-7), GFAP, SOX10, EMA and CD34. Diffuse neurofibroma shows expression of melanocytic markers like S-100, Melan A, HMB-45[9].

HMB-45 : Human Melanoma Black -45.
NSE : Neuron specific enolase.
GFAP : Glial fibrillary acidic protein.
MiTF: Microphthalmia transcription factor.