Multiple cutaneous neuromas: A case report.

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ABSTRACT:

SUVAPHAN S, TANTANASRIGUL P, SUDTIKOONASETH P. MULTIPLE CUTANEOUS NEUROMAS: A CASE REPORT. THAI J DERMATOL 2017;33: 313-321.

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A palisaded encapsulated neuroma (PEN) is a benign nerve sheath tumor, which is classified as a true neuroma based on the ratio (1:1) of axons to Schwann cells. This type of neuroma typically occurs as a solitary papular lesion, with a predilection for the central area of the face. Multiple mucosal neuromas are often associated with multiple endocrine neoplasia type 2b (MEN2b) and may be related to *PTEN* hamartoma tumor syndrome (PHTS). Multiple idiopathic cutaneous neuromas are unusual events, which occur spontaneously. We describe the case of a 14-year-old boy who presented with an eight-year history of multiple asymptomatic nodules. The number of nodules had increased over time. Prior to presenting to the clinic, histopathological analyses of three skin biopsy specimens had revealed similar findings, showing well-defined encapsulated spindle-shaped tumor cells in interlacing fascicles, with artefactual clefts. An immunohistochemical analysis revealed findings consistent with a diagnosis of PEN. Given the clinical presentation and the results of the histological analyses, a diagnosis of multiple cutaneous neuromas was established. Further endocrine work-up revealed the absence of MEN2b features.

Key words: Multiple idiopathic cutaneous neuromas, multiple endocrine neoplasia 2b syndrome, palisaded encapsulated neuroma

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บทคัดย่อ:

สลิล สุวพันธ์ พิมพา ตันธนศรีกุล ปุณวิศ สุทธิกุลณเศรษฐ์ รายงานผู้ป่วยที่มีภาวะเนื้องอกระบบประสาทส่วนปลายบริเวณผิวหนังเป็นจำนวนมาก วารสารโรคผิวหนัง 2560; 33: 313-321.

สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

เนื้องอกชนิดดีของระบบประสาทส่วนปลายที่ผิวหนังชนิดมีปลอกหุ้ม (palisaded encapsulated neuroma) มีลักษณะอาการทางคลินิกคือ ก้อนนูนขนาดเล็กพบบริเวณใบหน้า มักเกิดขึ้นเพียงแค่ก้อนเดียว การตรวจพบเนื้องอกชนิดนี้ที่ผิวหนังเป็นจำนวนมาก สามารถพบได้ร่วมกับโรคกรรมพันธุ์บางชนิด เช่น กลุ่มโรคเนื้องอกที่ระบบต่อมไร้ท่อชนิด 2b (multiple endocrine neoplasia type 2b) กลุ่มโรคเนื้องอกที่มีความผิดปกติที่ *PTEN* gene (*PTEN* hamartoma-tumor syndrome) และ พบได้น้อยสุดคือ ชนิดไม่ทราบสาเหตุ (Multiple idiopathic cutaneous neuromas) รายงานฉบับนี้ เป็นการนำเสนอผู้ป่วยเด็กชายอายุ 14 ปี มาด้วยอาการก้อนนูนบริเวณลำตัวเป็นจำนวนมาก ทำการวินิจฉัยทางชิ้นเนื้อจากผิวหนังบริเวณหลากหลายตำแหน่ง ลักษณะทางพยาธิวิทยาและการย้อมพิเศษ เข้าได้กับเนื้องอกชนิดดีของระบบประสาทส่วนปลายที่ผิวหนังชนิดมีปลอกหุ้ม(palisaded encapsulated neuroma) จากอาการทางคลินิกและผลพยาธิวิทยาผู้ป่วยจึงได้รับการวินิจฉัยเป็น ภาวะเนื้องอกชนิดดีของระบบประสาทส่วนปลายบริเวณผิวหนังเป็นจำนวนมาก (multiple cutaneous neuromas) ทำการตรวจเพิ่มเติมยังไม่พบลักษณะของกลุ่มโรคเนื้องอกที่ระบบต่อมไร้ท่อชนิด 2b (multiple endocrine neoplasia type 2b)

คำสำคัญ: เนื้องอกชนิดดีของระบบประสาทส่วนปลายบริเวณผิวหนัง, โรคเนื้องอกต่อมไร้ท่อหลายระบบชนิด 2b

Case report

A 14-year-old boy presented with an eight-year history of multiple asymptomatic nodules. A number of nodules had increased over time. The lesions were distributed over the patient's trunk and back. No associated symptoms were noted. He denied history of chronic constipation. His childhood development milestones were reached normally. His parents are healthy and non-consanguineous couple. No history of abnormal mucocutaneous lesions, thyroid cancer, gastrointestinal tract polyps or other malignant neoplasms was reported in his family.

On physical examination, the patient did not appear to have Marfanoid habitus (e.g., high arched palate, pectus excavatum, dolichostenomelia and arachnodactyly), thyroid gland enlargement, or palpable thyroid nodules. Approximately 15 flesh-colored nodules (5–15 mm) were detected on the patient's trunk, back and proximal limbs **(Fig. 1)**. No abnormal papillomatous papular lesions were found on the patient's face, palms, or oral mucosa. Genital macular pigmented lesions were not detected. His head circumference of 56cm was <97th percentile and the ratio of arm span and height was within normal range. On eye

examination, the thickness of medullated corneal nerve was absent under slit lamp examination. The other physical examination was unremarkable.

The skin biopsies of separate sites were performed. Prior to presentation at the clinic, histopathological analyses of three skin biopsy specimens had revealed similar findings. The results revealed well-encapsulated proliferative nerve bundles in interlacing fascicles, with artefactual clefts and without Verocay bodies **(Fig. 2)**. No pleomorphism was detected. Spindle cells showed immunoreactivity to S-100 **(Fig. 3A)**. Neurofilaments (NF) immunostaining which visualize axonal content in the tumor was positive staining. **(Fig. 3B)**. A thin layer of epithelium surrounding the tumor was demonstrated by epithelial membrane antigen (EMA) **(Fig. 3C)**. The overall features suggested a palisaded encapsulated neuroma (PEN). Given the clinical presentation and the results of the histological analyses, a diagnosis of multiple cutaneous neuromas was established.

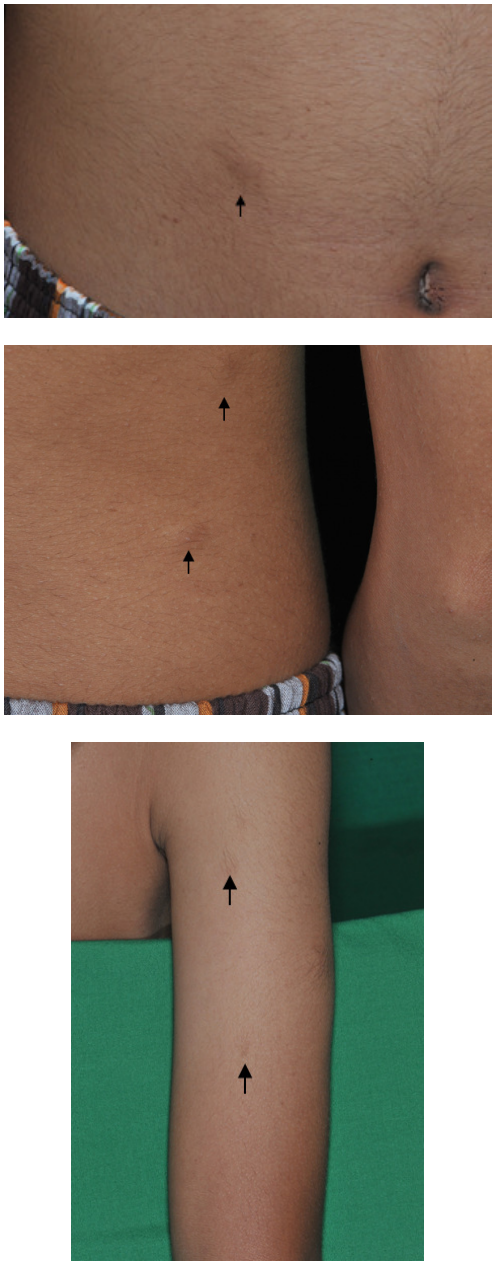

Figure 1 Several 5-15-mm.,flesh-colored nodules appear on the trunk (a), back (b) and proximal limbs(c)

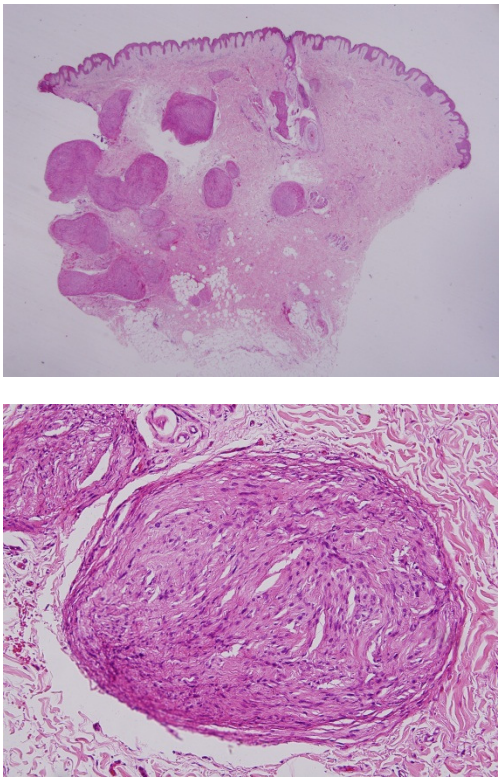

Figure 2 Histological examination revealed well-circumscribed nodules in the dermis. The borders of the tumors are sharply demarcated surrounding by a thin layer of epithelium. The nerve bundles arranging in intersecting fascicles are composed of proliferations of spindle-shaped cells with wavy, basophilic nuclei and poorly delineated eosinophilic cytoplasm. The characteristic separated clefts are prominent.

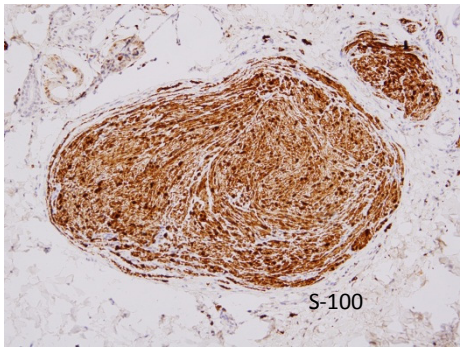

Fig 3(A)

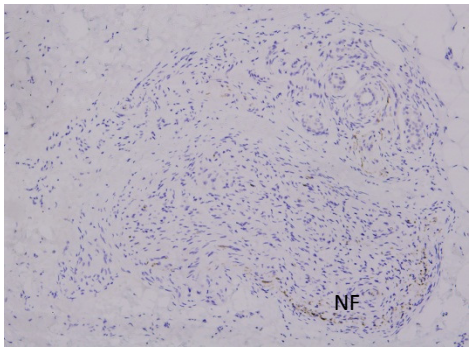

Fig 3(B)

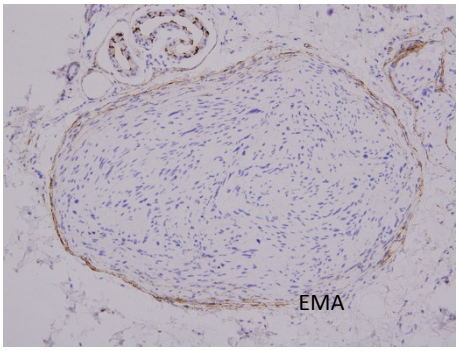

Fig 3(C)

Figure 3 Immunohistochemical analysis.
(a) Schwann cells (S-100 protein staining).
(b) Several axons (neurofilament staining).
(c) Perineural cells (epithelial membrane antigen staining).

Further investigations were done to exclude multiple endocrine neoplasia type 2b (MEN2b). Thyroid ultrasound sonography revealed normal result. Laboratory tests (a complete blood cell count, thyroid function tests, serum calcium and calcitonin levels, and urinalysis) were within normal limits. A cytological examination to detect abnormalities of the *RET* proto-oncogene, which identified over 99% of individuals with MEN2b[1], and *PTEN* gene were not performed due to financial constraints.

Although systemic abnormalities were not detected in our case, the potential role of unknown mutations in the distinctive clinical presentation could not be excluded. Long-term follow up is necessary to detect the clinical abnormalities.

Discussion

Multiple cutaneous neuromas are rare conditions. According to the literature, they may be related to multiple endocrine neoplasia type 2b (MEN2b), *PTEN* hamartoma tumor syndrome (PHTS) and be idiopathic.[2-4] Multiple mucosal neuromas are one of characteristic features of MEN2b [5] and generally present at birth or occur in early childhood.[6] MEN2b is caused by germline mutations in the *RET* proto-oncogene.[7] The syndrome consists of multiple mucosal neuromas, medullary thyroid carcinomas, and pheochromocytomas.[6,7] Marfanoid habitus, gastrointestinal ganglioneuromatosis, and corneal nerve hypertrophy may be present in patients with MEN2b syndrome.[6,7] Along with MEN2b, some articles[2] revealed that cutaneous neuromas may be the earliest cutaneous signs of PHTS; while, classic mucocutaneous manifestations (e.g., facial and oral papillomatosis, trichilemmoma, and palmoplantar keratosis) of PHTS tend to appear in late adolescence or early adulthood.[2] These neuromas have a predilection for the extremities. The presence of multiple neuromas especially involving acral sites prove to be more specific for PHTS.[2] However, neuromas are not common presentation in PHTS.

Table 1. Prior reports of multiple idiopathic cutaneous neuromas.

Reports	Age(y)/Gender	Neuroma findings/Locations	Mucosal neuromas	Other cutaneous findings	Other systemic findings	Genetic analysis
Our case	14/Male	15 nodules /Trunk ,back and proximal limbs	None	None	None	Not performed
Lee et al.,[15] (2016)	48/Female	Multiple zosteriform nodules /Distribute over the cervical spinal nerve (C2, 3)	None	None	None	No documents

Table 1 Prior reports of multiple idiopathic cutaneous neuromas. (ต่อ)

Reports	Age(y)/Gender	Neuroma findings/Locations	Mucosal neuromas	Other cutaneous findings	Other systemic findings	Genetic analysis
Liu et al.,[4] (2016)	56/Male	50 papules and nodules /Whole body	None	None	None	No documents
Julien et al.,[1] (2015)	48/?	Multiple linear raised papules /Back and forearms	None	None	A benign 4-mm thyroid nodule.	No mutation in exons 10,11,13,14,15 and 16 of *RET*
Omori et al.,[14] (2014)	7/Female	12 tender papules /Palm and soles	None	None	None	No mutation in exons 13,15 and 16 of *RET*
Halder et al.,[12] (2013)	30/Female	Multiple zosteriform nodules /Distribution over the ophthalmic division of the trigeminal nerve	None	None	None	No documents
Misago et al.,[8] (2013)	50/Male	100 papules and nodules /Whole body and acral sites	Lips and perioral area	None	None	No mutation in either *RET* or *PTEN* genes
Lee et al.,[7] (2013)	45/Female	Several papules /Face and acral sites	None	None	None	No documents
Moore et al.,[3] (2010)	7/Female	3 papules /Nose and one on each foot	None	None	None	No mutation in exons 10,11,13,14,15 and 16 of *RET*
Jokinen et al.,[13] (2010)	13/Female	Multiple papules /Bilateral hands	None	None	None	No documents
Truchot et al.,[2] (2001)	53/Female	25 papules /Whole body	Lip	None	None	No mutation in exons 15 and 16 of *RET*
Holm et al.,[5] (1973)	70/Male	Multiple linear raised papules /Trunk and proximal upper extremities	None	None	Slight enlarge-ment of thyroid gland	No documents

Multiple cutaneous neuromas as an isolated cutaneous presentation and idiopathic caused has been described. The characteristic features of multiple idiopathic cutaneous neuromas were described by Misago et al..[8] These features included (1) adult onset; (2) whole-body involvement with a predilection for the lips and acral sites; (3) isolated clinical features without

any other abnormalities; and (4) the absence of germline mutations in either the *RET* proto-oncogene or *PTEN* gene.[8] Prior reported cases of multiple idiopathic cutaneous neuromas were summarized in **Table 1**, the patients with an age ranges of 7-70 years had a predilection, particularly on female. The neuroma lesions occurred in various sites. Most cases[4,8,9] had neuromas in a whole body. All cases had no relevant systemic findings with PHTS and MEN2b. Analyses of the *RET* proto-oncogene and/or *PTEN* gene showed negative result in five cases. The clinical variant of multiple idiopathic cutaneous neuromas presenting in the linear lesions[1,5,10,11] and zosteriform[12,13] were also demonstrated. Baykal et al.[11] and Guillet et al.[10] described a possible association of multiple idiopathic cutaneous neuromas presenting in the linear raised papules with MEN2b. However, multiple idiopathic cutaneous neuromas could possibly occurred on childhood onset according with these reported cases.[3,14,15] All of these presented cases did not have any characteristic features of PHTS and MEN2b which were confirmed by the negative results of *RET* proto-oncogene mutation.[3,14,15]

Histologically, sporadic neuroma (palisaded encapsulated neuroma; PEN) appears as well-encapsulated proliferative nerve bundles in interlacing fascicles, with characteristic artefactual clefts.[16] The tumor is composed of axons and surrounded by wavy Schwann cells, which are visualized by immunohistochemical staining. PEN is positive for antibodies to the S-100 protein and neurofilaments(NF) immunostaining, which is demonstrats in the Schwann cells and axonal component, respectively. Epithelial membrane antigen staining (EMA) can be used to detect a thin layer of epithelium surrounding the tumor.[17, 18] The histopathology of neuromas in both PTHS and MEN2b is nearly identical[19]. The findings are quite similar to those seen in sporadic PEN, but the nerve fascicles tend to be scattered in the dermis as compared with the large mass of interlacing fascicles observed in PEN.[19] The histopathology of an individual lesion in cases of multiple idiopathic cutaneous neuromas show findings of cutaneous neuromas observed both in MEN2b and sporadic PEN.[19] This suggests that in terms of their histogenesis, multiple idiopathic cutaneous neuromas may be related to MEN2b.[16, 19]

In conclusion, we demonstrated the case of multiple cutaneous neuromas in childhood onset involved the extremities and trunk. Base on the prior reports, it could either relate to the syndrome or idiopathic which requires further investigations. Although the analyses of genetic sequencing of the common *RET* and *PTEN* gene mutations were not performed in our case, we instead did the complete physical and

laboratory examinations to detect any possibilities related to abnormalities as mentioned above. As for the age of our patient, the absence of characteristic cutaneous signs of PHTS (e.g., facial and oral papillomatosis, trichilemmoma, palmoplantar keratosis and macrocephaly) was affirmed; these negative examination results did not fulfill the PHTS criteria in our patient. We also performed a complete endocrine examination with our case to exclude the MEN2b syndrome. The thyroid ultrasonography revealed the normal result. The other endocrine work-up results were unremarkable. Our case was not definitely complied with MEN2b criteria. However, under such circumstance, we cannot eliminate other unknown mutations or mosaicism which can potentially be the cause of these distinctive clinical presentations as well as presenting an incomplete form of MEN2b and PHTS. We suggest that this presented case is unique and will require continued monitoring for systemic changes.

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