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Phacomatosis pigmentokeratotica: two cases series of a neurocutaneous rarity from Indonesia

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ABSTRACT

Phacomatosis pigmentokeratotica (PPK) is a distinct epidermal naevus syndrome. The syndrome is characterized by the coexistence of an organoid naevus with sebaceous differentiation arranged along Blaschko's lines, a papular naevus spilus arranged in a checkerboard pattern, in association with other extracutaneous anomalies. We report on two cases of PPK. The first case was an 11-year-old girl with sebaceous naevus on the right side of the body following the lines of Blaschko present since birth, whereas a papular naevus spilus involving the dorsal area of the neck was noted at 8 years of age. The second case was a 15 year-old girl presented with sebaceous naevus on her face and neck and papular naevus spilus involving left side of her chest. Electroencephalography (EEG) of both cases revealed abnormal irritative epileptiform waves, and brain mapping showed symmetrical structures and no focus. The diagnoses of our two cases were based on clinical pictures of the coexistence of sebaceous naevus arranged along Blaschko's lines, a papular naevus spilus arranged in a checkerboard pattern, and EEG anomalies. To our knowledge, these cases were first reported in Indonesia. The association with various extracutaneous manifestation is often, as well as the possibility of malignant transformation. Hence a close follow-up of PPK patients is important, which may help in early recognition of the development of extracutaneous anomalies and the possibility of malignant transformation.

ABSTRAK

Phacomatosis pigmentokeratotica (PPK) merupakan sindrom nevus epidermal yang unik. Sindrom ini ditandai secara khas oleh adanya nevus organoid dengan diferensiasi sebaseus yang tersusun mengikuti garis Blaschko, nevus spilus tipe papular yang tersusun seperti pola kotak catur, disertai dengan anomali ekstra kutan lain. Kami melaporkan dua kasus PPK. Kasus pertama adalah seorang anak perempuan usia 11 tahun dengan nevus sebaseus pada sisi kanan tubuh yang nampak sejak lahir dan mengikuti garis Blaschko, disertai dengan nevus spilus tipe papular pada leher sisi belakang yang disadari ketika usia 8 tahun. Kasus kedua adalah seorang anak perempuan usia 15 tahun dengan nevus sebaseus pada wajah dan leher, disertai dengan nevus spilus pada dada kiri. Pemeriksaan *electroencephalography* pada kedua pasien menunjukkan gelombang *abnormal irritative epileptiform*, dan *brain mapping* menunjukkan *symmetrical structures* dan tidak ada fokus. Diagnosis pada kedua pasien ditegakkan berdasarkan gambaran klinis koeksistensi nevus sebaseus yang tersusun mengikuti garis Blaschko dan nevus spilus tipe papular yang tersusun dengan pola kotak catur serta anomali EEG. Sepanjang pengetahuan kami, kasus ini adalah yang pertama dilaporkan di Indonesia. Pada PPK sering ditemukan manifestasi ekstrakutan dan perubahan kulit ke arah keganasan, oleh karenanya penting dilakukan f*ollow-up* rutin pada pasien PPK untuk membantu mengenali secara dini perkembangan anomali ekstrakutan dan perubahan ke arah keganasan.

Keywords:
checkerboard pattern
lines of Blaschko
mosaicism
organoid naevus
papular naevus spilus
sebaceous naevus

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INTRODUCTION

The term phacomatosis pigmentokeratotica (PPK) was delineated in 1996 for a specific "twin naevus" syndrome characterized by the co-occurrence of an epidermal naevus of a non-epidermolytic organoid type arranged along Blaschko's lines,[1,2] and a papular naevus spilus arranged in a checkerboard pattern, associated with various neurological, skeletal and ophthalmological abnormalities.[3,4] The disease was previously explained as "twin spot" mosaicism due to post-zygotic crossing-over of two homozygous recessive mutations,[1] however it has recently been shown that the disease derive from one postzygotic activating RAS mutation.[5]

Approximately 40 cases are reported in the literature, a majority manifesting extracutaneous abnormalities. Some published cases reported malignant transformation of cutaneous components of PPK; i.e. the development of basal cell carcinoma from the naevus sebaceous.[6-12] The development of syringocystadenoma papilliferum, and trichilemmoma carcinoma from the naevus sebaceous,[12] and the development of malignant melanoma from the papular naevus spilus.[2,9]

We herein describe two additional cases, first reported in Indonesia with this rare condition and emphasize the importance of close follow-up of PPK patients which may help in early recognition of the development of extracutaneous anomalies and the possibility of malignant transformation.

CASE 1

An 11-year-old girl presented from birth a large sebaceous naevus (SN) on the right side of the body following the lines of Blaschko and a papular naevus spilus involving the dorsal area of the neck arranged in a checkerboard pattern which was noted at 8 years of age. She is the second child of healthy nonconsanguineous parents, was born at term from an uncomplicated pregnancy and had an unremarkable family history. On physical examination, there was a linear epidermal naevus on the right side of her body including the scalp, face, neck, trunk, arm, and leg. The lesions stopped at the midline and were intermingled on the left side of the neck with a papular naevus spilus arranged in a checkerboard pattern (FIGURE 1 A; B and 2).

FIGURE 1. A. Face frontal ; B. Face lateral view show sebaceous naevus following lines of Blaschko

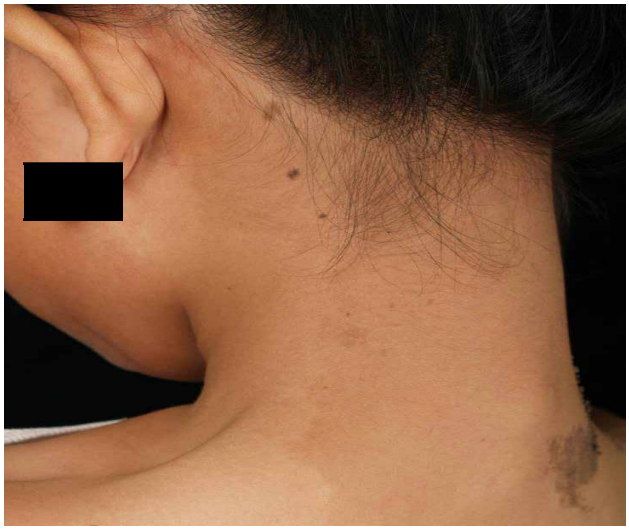

FIGURE 2. Neck lateral view show speckled lentiginous naevus arranged in a checkerboard pattern

The right side of the trunk was diffusely involved by the papular naevus spilus and showed a similar intermingling of the two types of naevi (FIGURE 3 A and B). Electroencephalography revealed abnormal irritative epileptiform waves, and brain mapping showed symmetrical structures and no focus. Psychological examination showed a normal mental state and intelligence. Ophthalmological evaluation disclosed no abnormalities, and the patient's development and intelligence were normal. The girl's hearing was impaired because of the epidermal naevus involving the ear canal. So far, the parents refused permission for a histopathological examination of the cutaneous lesions. The diagnosis of PPK was based on clinical features.

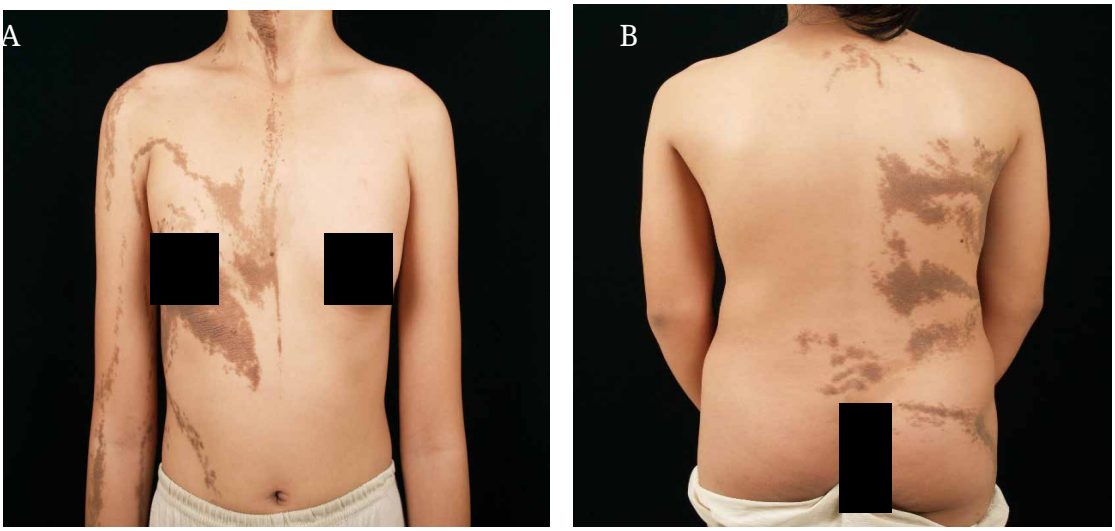

FIGURE 3. A. Trunk frontal; B. Trunk dorsal view showed sebaceous naevus following Blaschko lines

CASE 2

A 15-year-old girl had an epidermal naevus on the face and neck following the lines of Blaschko which was present since birth. She is the first child of healthy nonconsanguineous parents, was born at term from an uncomplicated pregnancy and had an unremarkable family history. Postnatal development was normal with no evidence of seizures. At 8 years of age she came to us with linear epidermal naevus on the face and neck. On the face there was sebaceous naevus following Blaschko lines (FIGURE 4A) and linear epidermal naevus on the neck and back which is intermingled with various sized light brownish macules and dark brownish papules (papular naevus spilus) (FIGURE 5A). Electroencephalography at that time revealed abnormal irritative epileptiform waves, and brain mapping showed symmetrical structures and no focus. Psychological examination showed a normal mental state and intelligence. Ophthalmological evaluation disclosed no abnormalities, and the patient's development and intelligence were normal. The parents refused permission for a histopathological examination of the cutaneous lesions. The diagnosis of PPK was based on clinical features. The patient was lost of follow up but returned to our clinic at 15 years of age, after underwent several staged partial excisions of the extensive sebaceous naevus on face in other district hospital (FIGURE 4B). Extensive epidermal naevi on her neck and back which is intermingled with papular naevus spilus were noted (FIGURE 5B)

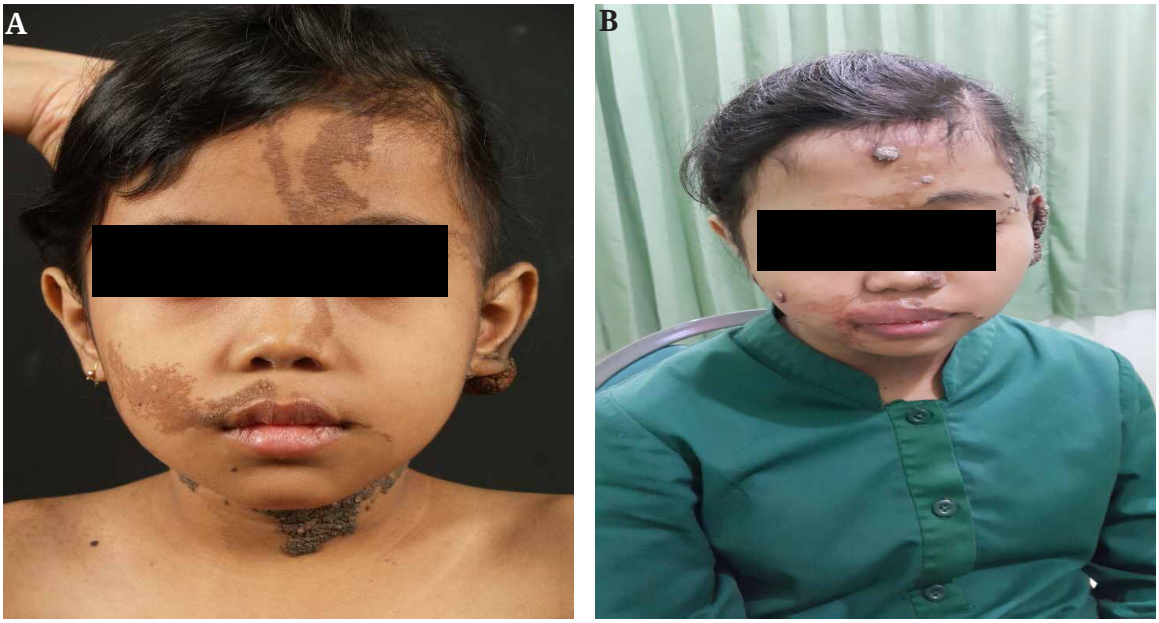

FIGURE 4 A. Linear epidermal naevus on the face following the lines of Blaschko (age 8 years old); 4B. Linear epidermal nevus on the face after serial of excision (age 15 years old)

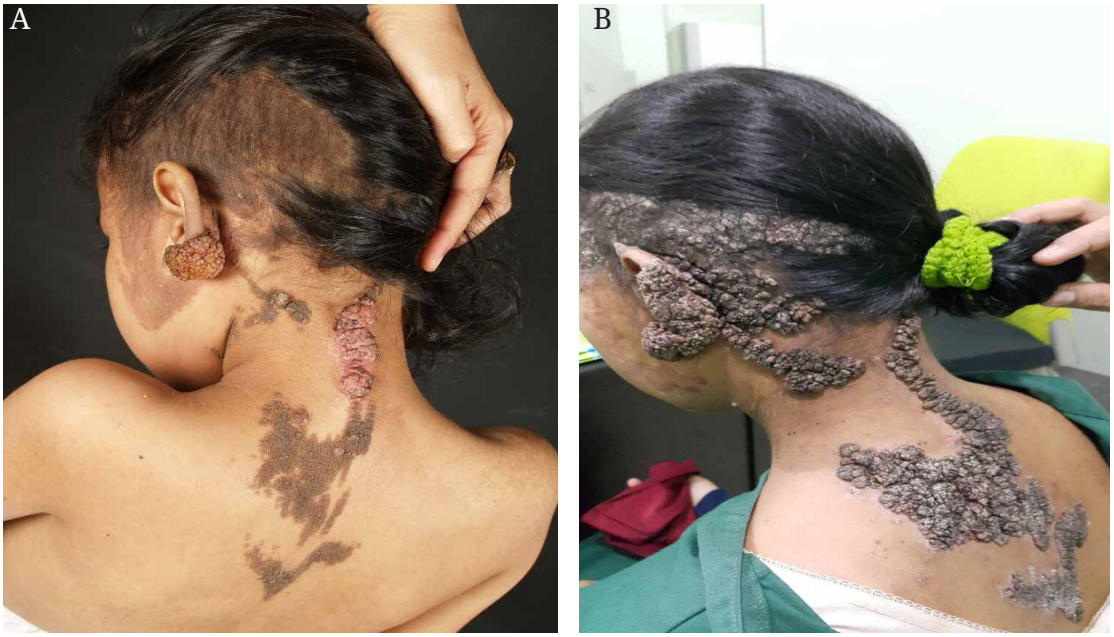

FIGURE 5. Linear epidermal nevus on the neck which is intermingled with speckled lentiginous nevus. A. age 8 years old, B. age 15 years old.

DISCUSSION

Phacomatosis pigmentokeratotica was first described by Happle *et al*. to describe a distinct type of epidermal naevus syndrome which arises due to genetic mosaicism.[1] The syndrome is rare. To date only approximately 40 cases are reported in the literature, a majority manifesting extracutaneous abnormalities i.e. neurological, skeletal and ophthalmological. All cases reported so far are sporadic. PPK is an example of autosomal recessive mutations that are usually lethal but survive by mosaicism.[13]

Phenotypic of PPK

The syndrome presents the striking cutaneous findings of two different types of nevi i.e. epidermal naevus with sebaceous differentiation arranged along the lines of Blaschko, and a papular naevus spilus arranged in a checkerboard pattern. The two types of naevi are predominantly ipsilateral or contralateral, but may also be bilaterally distributed.[14] The association with various extracutaneous defects such as neurological, skeletal, or ophthalmological abnormalities may likewise occur. Neurological features noted include mild mental disability, seizures and deafness. Hemiatrophy with variable muscle weakness, dysaesthesia, and hyperhidrosis were observed in the region of the papular naevus spilus.[13] Associated skeletal abnormalities include kyphosis/scoliosis and hypertrophy of the ipsilateral leg.[13,15] Ophthalmologic defects such as strabismus and ptosis have been reported to be associated with the syndrome.[2]

Slight hyperhidrosis was present on our first patient. Abnormal irritative epileptiform waves were found in EEG examination of both patients, however no clinical seizures were noted. Both patients had normal mental state and intelligence. All other associated diseases could be excluded.

Genetic background of PPK

Previously the coexistence of the two cutaneous lesions in PPK is explained by a genetic mechanism known as the twin-spot phenomenon or didymosis.[1,13] The hypothesis is based on the concept of somatic recombination due to an early post-zygotic mutational event. Two different autosomal recessive mutations (papular naevus spilus and organoid naevus with sebaceous differentiation) must be located on either of a pair of homologous chromosomes. The embryo is therefore doubly heterozygous. During early embryogenesis an event of post-zygotic crossing-over may give rise to two different homozygous populations of cells forming two different mosaic patterns. The distinct mosaic spots tend to be arranged in close proximity to each other and thus are called 'twin spots' or didymosis.[13] Either papular naevus spilus or naevus sebaceus can be separately transmitted as paradominant trait.[16] These separately transmitted component would only become manifest when during embryogenesis a postzygotic mutation occurred, giving rise to loss of heterozygosity resulting in a homozyous or hemizygous cell population that survives in close proximity with the phenotypically normal heterozygous cell population, and representing a paradominant traits.[16]

Recently, however, molecular evidence was postulated that the paired nevi (both the naevus sebaceous and papular naevus spilus) originate from one single multipotent progenitor cell being heterozygous for a HRAS (harvey rat sarcoma viral oncogene homolog) mutation.[5] The postzygotic somatic mosaicism of an activating RAS (rat sarcoma viral oncogene homolog) mutation was identifed in two patients with Schimmelpenning syndrome and a naevus sebaceus.[5] Hence, HRAS mutation is thought to occur at the level of an ectodermal multipotent progenitor cell that gives rise to both keratinocytes and melanocytes, explaining the heterogenous components of PPK: sebaceous naevus and papular naevus spilus.[5]

In this new hypothesis, the respective mutation in the multiple progenitor cells gives rise to both cutaneous and extracutaneous abnormalities noted in PPK. Moreover, the timing of the mutation during embryogenesis and differentiation are crucial determining the phenotype.[5] Hence, the twin-spot theory can no longer be sustained and the disorder should be regarded as a "pseudodidymosis".[17]

Management

Management of the newborn with extensive epidermal naevus following the lines of Blaschko begins with a thorough physical examination to document other extracutaneous anomalies such as neurological, skeletal or ophthalmological abnormalities. A multidisciplinary approach is required. The dermatologist, pediatrician, neurologist, ophthalmologist, and geneticist should be involved. Annual clinical follow-up is recommended as malignant transformation has been reported in both naevus components, and to observe the possibility of developing extracutaneous anomalies. We educate our patients to visit doctor every 6 months to check the possibility of malignant transformation.

Genetic counseling is an important aspect of management of the PPK. Advances in our molecular understanding of this syndrome may allow for more specific risk analysis in the future.

CONCLUSION

The coexistence of a papular naevus spilus in a checkerboard pattern and a sebaceous naevus following

Blaschko lines suggested a diagnosis of PPK. To our knowledge, our cases were first reported in Indonesia. Both patients have an abnormal EEG showing irritative epileptiform waves. A close follow-up of PPK patients is important, as in our cases with abnormal EEG, it may help in early recognition of potentially developing seizure in life. The potential melanoma precursor role of naevus spilus and development of basal cell carcinoma from the naevus sebaceous raises important issues of clinical recognition and management.

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