

CLINICAL REPORT

Phacomatosis Pigmentokeratolica with Nephroblastoma and Juvenile Hypertension

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Phacomatosis pigmentokeratolica is characterized by the coexistence of an organoid epidermal naevus, following Blaschko's lines, and a large speckled lentiginous naevus, typically arranged in a chequerboard pattern. This entity has been isolated from the group of epidermal naevus syndromes and is frequently associated with extracutaneous anomalies. We report here the first observation of phacomatosis pigmentokeratolica associated with nephroblastoma. In addition to this paediatric renal tumour, the coexistence of juvenile arterial hypertension suggests an associated vascular defect. The link between the extracutaneous manifestations and cutaneous twin spot phenotype is discussed. Key words: epidermal naevus; mosaicism; cancer.

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Phacomatosis pigmentokeratolica (PPK) has been identified by Happle as a specific entity among the different forms of epidermal naevus syndromes (ENSs) (1). It is characterized by the coexistence of an epidermal naevus following Blaschko's lines and usually showing sebaceous differentiation, and a large speckled lentiginous naevus, typically arranged in a chequerboard pattern. This syndrome is an example of cutaneous mosaicism that is thought to be related to twin spotting phenomenon (2), as it has yet been suggested for phacomatosis pigmentovascularis (3). The supposed pathophysiology is a postzygotic crossing-over (or somatic recombination) in a doubly heterozygous embryo at an early stage, resulting in two different clones of neighbouring cells. Further studies, including genetic and molecular characterization of cutaneous keratinocytic and melanocytic clones, are needed to confirm this mechanism of mosaicism. PPK is either limited to the skin or associated with extracutaneous abnormalities. We report here for the first time an association of PPK with nephroblastoma, a malignant paediatric tumour that has sometimes been reported in cases of an unclassified ENS. A juvenile arterial hyper-

tension, which may be related to a spindly renal artery, is associated with this case. This observation confirms the importance of urological and vascular investigation in PPK. Furthermore, the laterality of the vascular and tumoural anomalies with either cutaneous component of the twin spot phenotype is discussed.

CASE REPORT

A 6-month-old boy was initially referred for juvenile hypertension. He was the last child of five siblings. He was born from healthy non-consanguineous Caribbean parents. At 4 months of age, a suspected abdominal mass led to the diagnosis of nephroblastoma of the left kidney. No visceral extension was detected. Chemotherapy (vincristine and actinomycin) and surgical resection of the left kidney were performed. During the follow-up, a cardiac arrest occurred, which resolved rapidly with inotropic drugs. Cardiac explorations showed an isolated atrial tachycardia, which was controlled with amiodarone. Two months after surgery, the patient was referred to our hospital because of persistence of the arterial hypertension. Computed tomographic angiography revealed a spindly right renal artery, apparently without stenosis. No aortic coarctation was detected. His blood pressure was controlled with medications including selective beta-blockers.

On the skin, he presented a verrucous epidermal naevus following Blaschko's lines (Fig. 1), mainly on the left side of the body, which extended to the neck and the left arm. A large light-brown macule affected the right side of the trunk. Histopathology of two skin biopsies showed, on one hand, a hyperkeratosis with papillomatosis and acanthosis, without sebaceous differentiation, and, on the other hand, an epidermal hypermelanocytosis. As the child presented a developmental and statural delay, brain magnetic resonance imaging, electroencephalography, and electrophysiological examinations (visual and auditory evoked potentials) were performed and considered to be normal. This delay improved with psychomotricity, and we therefore speculated that it was probably related to the long-term hospitalization. Ocular and musculoskeletal explorations were normal. Standard karyotype showed no chromosomal anomalies.



Fig. 1. Coexistence of a verrucous epidermal naevus, following Blaschko's lines, and a large light-brown macule, located on each side of the trunk (collection of the Department of Dermatology, Necker-Enfants Malades Hospital, Paris).

DISCUSSION

We describe here an unusual case of PPK associated with renal manifestation in the form of nephroblastoma on the left side and a potential abnormality of the right renal artery. The diagnosis of PPK was confirmed by clinical and histological presentation. It is important to note the absence of sebaceous differentiation in the biopsy of the epidermal naevus, obtained from the abdomen. Firstly, sebaceous glands may be lacking in biopsies obtained from outside the head and neck region. Secondly, the child may have been too young to show sebaceous differentiation (4). Another clinical and histological special feature in this case is the absence of the typical chequerboard pattern of the lentiginous naevus. However, in very young children, the papular speckles of naevus spilus papulosus, which is usually associated with PPK, may still be completely absent and appear later during childhood (5). The absence of melanocytes in the dermal part of the skin biopsy is in accordance with this clinical characteristic.

Since 1996, approximately 30 cases of this rare syndrome have been reported. Although cases without extracutaneous abnormalities have been described (6–9), musculoskeletal, ocular, neurological and vascular findings are commonly associated with this condition (10,

11). Our case of PPK is associated with nephroblastoma and a potential abnormality of a renal artery.

Malignancies are considered a risks of various ENS including PPK. These often involve the skin, with a risk of developing cutaneous tumours on each component of the syndrome (12, 13). An association of unclassified ENS and Wilms tumour has been mentioned by Solomon & Esterly (14), but these cases could not be characterized because of the lack of clinical data (15). Since this first description two other cases have been reported. Pawlaczyk et al. (16) reported an unclassified case of ENS associated with Wilms tumour. Courville et al. (17) reported the association of an epidermal naevus, neurofibromatosis type I and nephroblastoma. Though the neurofibromatosis type I in this case remains uncertain, because it does not fulfil the criteria for this diagnosis, the coexistence of an epidermal naevus, pigmentation abnormalities and Wilms tumour may correspond to our present case. However, the absence of follow-up and of histopathological examination of pigmented macules did not permit a clear conclusion. The diagnosis of ENS is ambiguous in many other cases reported until today (1). A large confluent light-brown macule reported in cases of ENS may correspond to the pigmentary component of a PPK (18). Carcinoma of the bladder (19), paratesticular rhabdomyosarcoma (20), digestive (salivary glands, oe-

sophageal and gastric) and mammary adenocarcinoma are reported in various types of ENS (20–23).

On the other hand, PPK may be associated with subcutaneous rhabdomyosarcoma (11), phaeochromocytoma (24), and spinal root tumours. Two cases of bladder involvement were reported: a rhabdomyosarcoma (18), and a leiomyoma (20).

Thus, our observation is a novel example of the urological and nephrological tropism for extracutaneous tumours in PPK. Nephroblastoma is, for the first time, clearly related to PPK. Although tumoural manifestations seem to be more often ipsilateral to the lentiginous naevus (11), nephroblastoma, in our case, is spatially associated with the epidermal naevus.

Moreover, Schimmelpenning syndrome, which is one of ENSs, seems to predispose to vascular abnormalities, such as aortic coarctation, renal artery stenosis, dilation or stenosis of pulmonary artery, valvular stenosis or insufficiency (21, 23, 25–27). Two cases of PPK have been reported associated with arterial hypertension: one case of extrinsic compression of renal artery by spinal roots tumour (28), and one case with both aortic stenosis and renal artery stenosis (29). Our observation is also associated with juvenile arterial hypertension, whose exploration revealed only a spindly right renal artery. While vascular defects are usually considered as a part of the organoid epidermal component of PPK (29), it is interesting to note that in our observation, the renal arterial abnormality is contralateral to the skin area involved by the epidermal naevus.

This observation emphasizes the wide clinical spectrum of PPK. The specific cutaneous features can be isolated or associated with extracutaneous manifestations.

A link between cutaneous mosaicism and tumours in other tissues has been suggested by the description of FGFR3 somatic mutations in epidermal naevus and in low-grade bladder tumours (30). It is also interesting to note that *Patched* and *TSC1* genes can be mutated in skin and bladder tumours (31, 32). Further studies are needed to determine in which way a postzygotic mutation at an early stage of embryogenesis could lead to different benign or malignant tumours in various organs.

In conclusion, we report here a new case of PPK. The clinical spectrum of extracutaneous manifestations in PPK is enlarged with the description of nephroblastoma and a juvenile arterial hypertension related to a spindly renal artery. Therefore we suggest that urological, renal and vascular explorations should be performed in patients with PPK for early detection of the most classical extracutaneous manifestations associated with this mosaic disorder.

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