Cutis Tricolor Parvimaculata: A Distinct Neurocutaneous Syndrome with Brain Involvement: Case Report

Kutis Trikolor Parvimakülata: Beyin Tutulumu Olan Farklı Bir Nörokutanöz Sendrom

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ABSTRACT Cutis tricolor is a skin disorder characterized by the coexistence of congenital hypo- and hyperpigmented maculer lesions, in close proximity to each other on a background of normal skin. Cutis tricolor parvimaculata describes the form consisting of smaller spots. These skin macules are called twin spotting and represent a part of a neurocutaneous malformation syndrome. Cutis tricolor may accompany various multisystem birth defects including craniofacial and brain abnormalities. It must be distinguished from other neurocutaneous syndromes such as tuberous sclerosis and neurofibromatosis. We described cutis tricolor parvimaculata in a 3-year-old girl, the reported youngest patient in the literature, with diffuse pigmentary spotting on the skin, facial anomalies, developmental delay and brain involvement.

Key Words: Neurocutaneous syndromes; malformations of cortical development; neuroectodermal tumors, primitive; skin pigmentation

ÖZET Kutis trikolor normal görünümlü cilt üzerinde birbirine çok yakın duran doğumsal hipo ve hiperpigmente maküler lezyonların bir arada bulunması ile karakterize bir cilt hastalığıdır. Kutis trikolor parvimakülata daha küçük lekeler içeren formunu tanımlar. Bu cilt makülleri ikiz noktalanma olarak adlandırılır ve nörokutanöz malformasyon sendromunun bir parçasını temsil eder. Kutis trikolor kraniyofasyal ve beyin anormalliklerini içeren çeşitli multisistemik doğumsal kusurlara eşlik edebilir. Tuberoz skleroz ve nörofibromatozis gibi diğer nörokutanöz sendromlardan ayırt edilmelidir. Literatürde bildirilen olgulara göre yaşça en küçük olan, ciltte yaygın pigmente lekelenmeleri, yüz anomalileri, gelişimsel gecikmesi ve beyin tutulumu bulunan üç yaşındaki bir kız çocukta kutis trikolor parvimakülatayı tanımladık.

Anahtar Kelimeler: Nörokütanöz sendromlar; kortikal gelişim malformasyonları; nöroektodermal tümörler, primitif; deri pigmentasyonu

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Cutis tricolor is an entity of a neurocutaneous syndrome that must be distinguished from tuberous sclerosis and neurofibromatosis. The characteristic lesions are hypo- and hyperpigmented macules, most likely representing twin spotting, located on normal skin.[1,2] The location and size of the macules are extremely variable.[3,4] Thus, it is clear that cutis tricolor is not one distinct clinical entity, it should rather be taken as a cutaneous sign of several different types of mosaicism.[5] Cutis tricolor parvimaculata describes the smaller disseminated twin spotting different from commonly known lesions.[5] Cutis tricolor may be associated with multisys-

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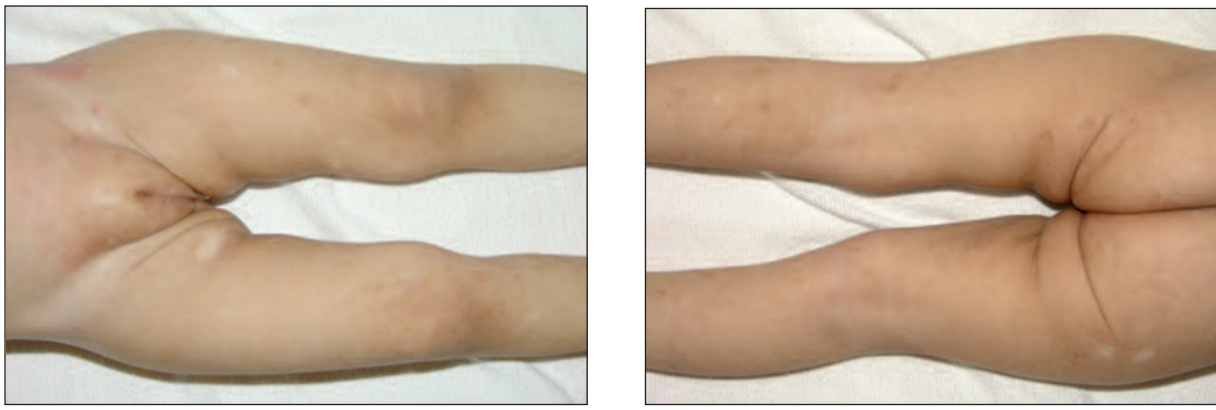
tem birth defects including craniofacial anomalies, mental and motor retardation, epileptic seizures and brain abnormalities.[2,3] There are only two reports of cutis tricolor in two different families that suggest autosomal dominant inheritance.[1,4] Here, we presented a 3-year-old girl diagnosed with cutis tricolor parvimaculata with unknown subcortical and periventricular lesions that revealed the brain involvement.

CASE REPORT

A 3-year-old girl was reffered to our clinic for developmental delay, weakness and fever. She was the full-term baby of nonconsanguineous healthy parents. The other two children of the family were all healthy. Physical examination of the parents revealed that the mother had a large nevus spilus on interscapular region. At birth, her weight was 2900 g (10-25% percentile), length was 51 cm (10-25% percentile) and head circumference was 35 cm (25-50% percentile). Prenatal history was unremarkable. Developmental milestones were delayed; head control was achieved at 4 months; she could sit without support and speak one or two words at the age of 2 years but she could not walk yet. However, she had no epileptic seizures.

On initial physical examination, her weight, height and head circumference were 8 kg, 71 cm, and 44 cm respectively and all were below the 3 percentile. Fever was 38.3°C and all other vital findings were normal. Examination of the skin revealed disseminated small and medium sized cafe-au-lait macules with hypochromic spots on the normal skin especially located on lower parts of the body (Figure 1A, B). Additional areas were interscapular region, neck and right shoulder. Hypopigmented macules were also seen around the mouth. The largest hyperpigmented patch was 2 cm and the hypopigmented was 0.3 cm in length. Face appearance was dysmorphic including hypertelorism, partial epicantal folds, backward rotated ears, deep nasal bridge with broad nostrils and scarce hairs (Figure 2). On abdominal examination, spleen was 3 cm palpable and the rest of the physical examination findings were normal. On laboratory examination, alanine aminotransferase was 224 mg/dL and aspartate aminotransferase was 305 mg/dL. Complete blood count (CBC) showed 2.4x10^9/L white blood cells, 0.4x10^9/L neutrophils, with haemoglobin level 13.8 g/dL, and platelet count 230x10^9/L. Peripheral blood smear revealed 24% Downey cells. Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgM serology was also positive. Other laboratory investigations including immunoglobuline levels, bacterial and viral serologies including HIV, and peripheral blood lymphocyte subtype analysis were normal. Blood, urine, stool and nasopharyngeal cultures were negative. The microscopic assessment of bone marrow aspiration was normal. Lumbar punction did not reveal any blood cells while the biochemical analysis of cerebrospinal fluid was normal. Tuberculin skin test-



A B

FIGURE 1A, B: Disseminated small and medium sized cafe-au-lait macules with hypochromic spots on the normal skin especially located on lower parts of the body.

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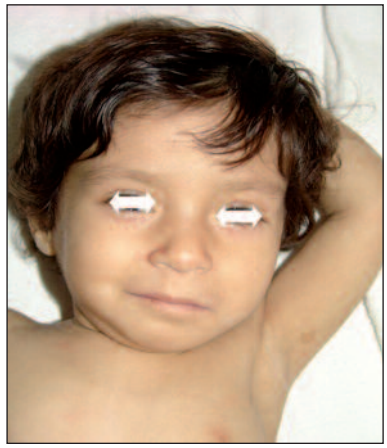

FIGURE 2: Dysmorphic face appearance including hypertelorism, partial epicantal folds, backward rotated ears, deep nasal bridge with broad nostrils, scarce hairs and hyperpigmented macula on left axilla.
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ing was unreactive and cultures for *M. tuberculosis* including the cerebrospinal fluid were negative. Ultrasonography of the abdomen showed moderate splenomegaly while the heart ultrasonography and chest radiography were normal. She was diagnosed with acute EBV infection and was monitored without any treatment. At discharge, all laboratory parameters were normal and the patient had no fever.

However, the cranial magnetic resonance imaging (MRI) scans revealed multiple, subcortical and periventricular lesions that were not suggestive of tuber, neurofibroma, tuberculoma or abscess (Figure 3A, B, C, D, E). The lesions were hypovascular in perfusion MRI (Figure 4A, B), while the diffusion was normal in diffusion MRI. In addition, proton magnetic resonance spectroscopy of the lesions showed choline and lipid peaks with decreased N-acetylaspartate. Solid lesions showed increased Cho/Cr ratio (Figure 5). However, biopsy was not possible due to their localizations; thus, the structures of the lesions could not be examined. In

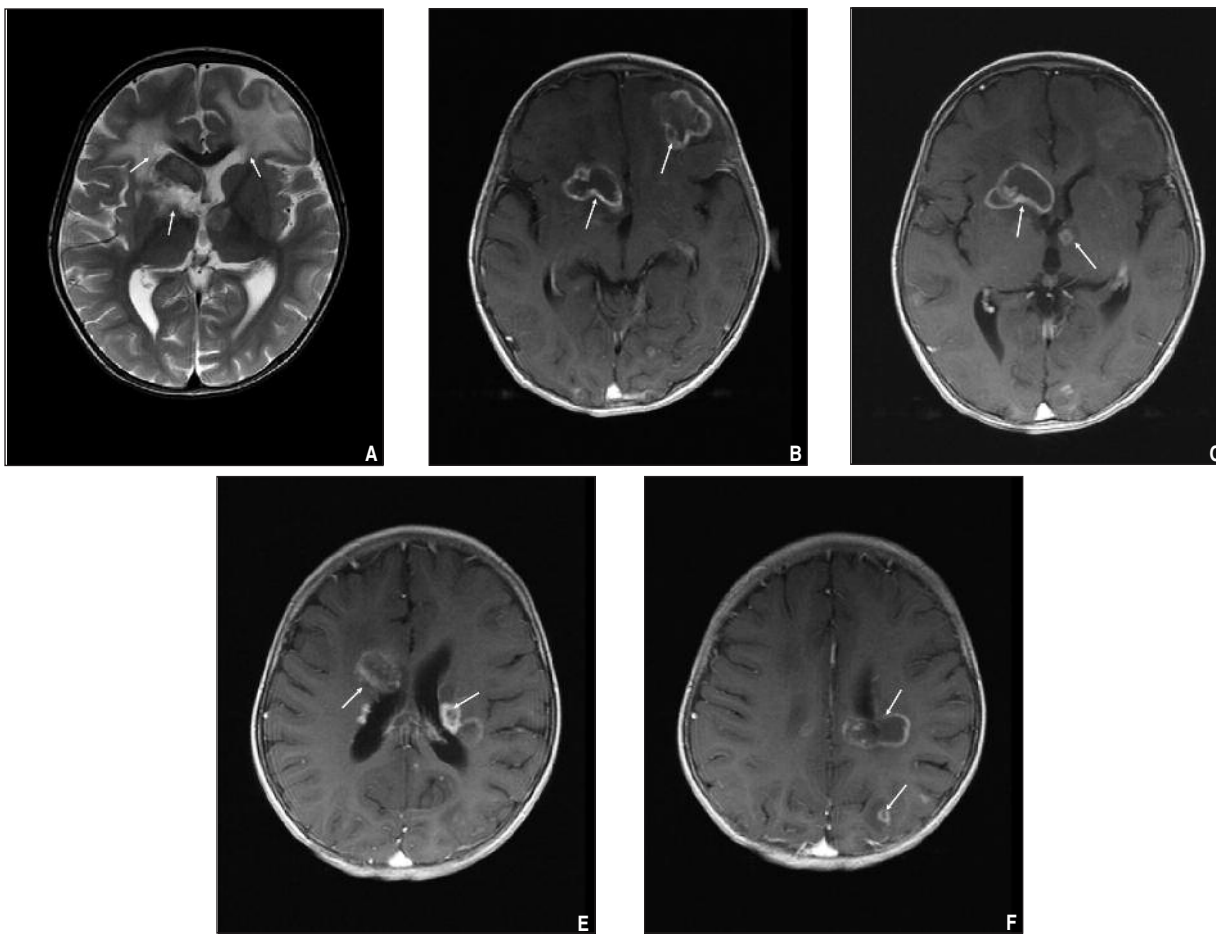
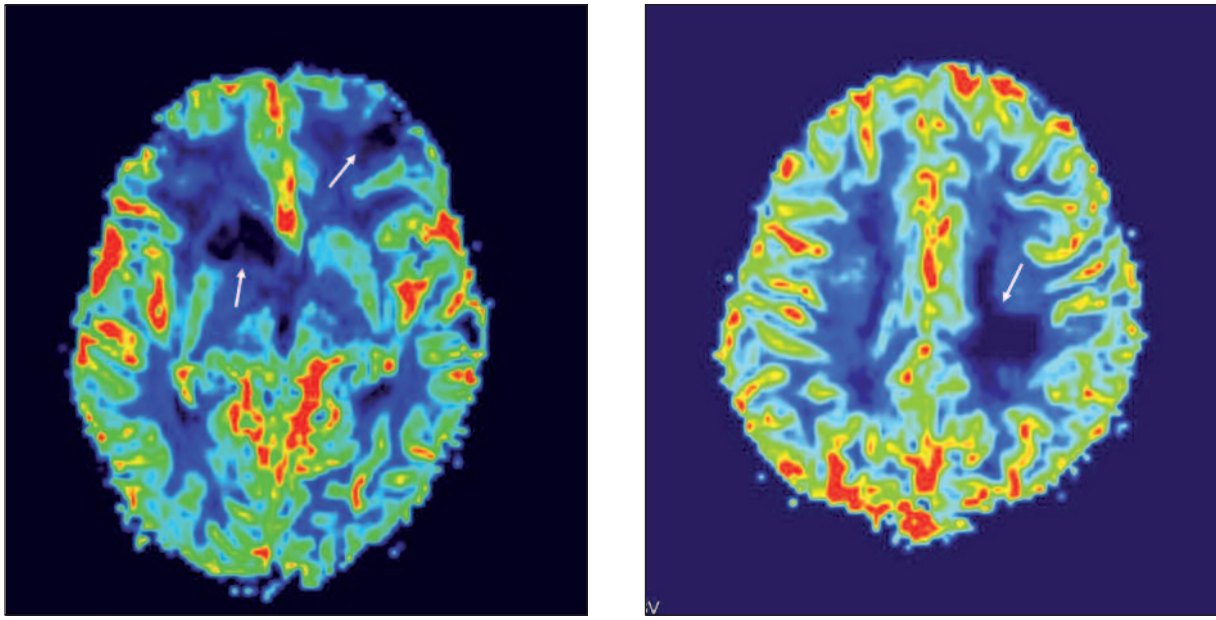


FIGURE 3: A. T2 weighted MR image shows hyperintense lesions. **B, C, D, E** Contrast enhanced T1 weighted MR images show multiple enhancing mass lesions.



A B

FIGURE 4A, B: The lesions (in periventricular region) were hypovascular in perfusion MRI (CBV: cerebral blood volume images).
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addition, repeated electroencephalographic (EEG) imaging studies showed slight left hemispheral asymmetry without any epileptic wave complexes. The retina examination for tuberous sclerosis was normal. The lesions enlarged, but the signal specialities did not change in repeated cranial MRI scans in the second month of discharge. However, the patient died due to aspiration pneumonia after the third month of discharge and the parents refused brain biopsy.

DISCUSSION

The reported case was categorized as cutis tricolor parvimaculata due to the presence of congenital disseminated small hypo-and hyperpigmented macules suggesting twin spotting on a background of normal skin. The term 'cutis tricolor' was first used by Happle et al. to describe hypo- and hyperpigmented skin patches associated with normally pigmented areas that result in three different colors.[2] Also parvimaculata type was described by Laralde and Happle suggesting smaller lesions than described in previous cases of cutis tricolor.[5] The incidence of this rare disease is not reported. Otherwise, the genetic locus and the inheritance pattern are not known exactly. But there are only two

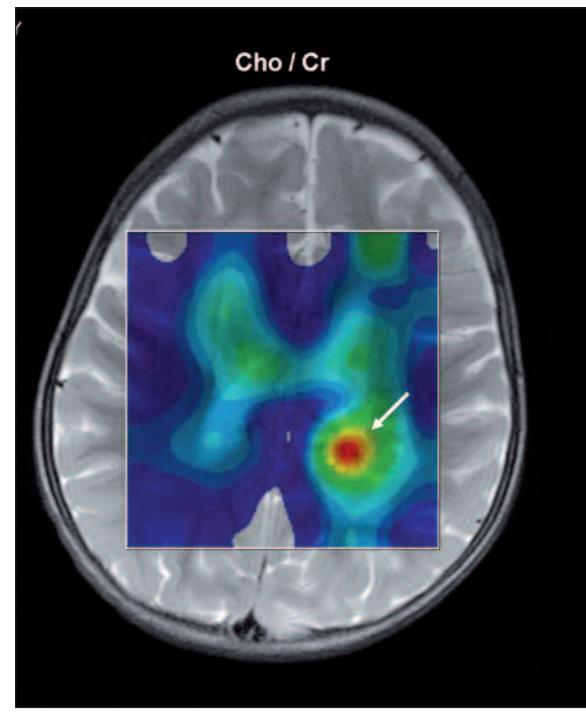

FIGURE 5: CSI (chemical shift image) spectroscopic map shows increased Cho/Cr ratio in left periventricular solid lesion.
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reports of cutis tricolor in two different families suggesting the autosomal dominant and paradominant inheritance.[1,4] The unknown underlying gene

locus may represent a hot spot for postzygotic recombinations, giving rise to multiple twin spots.[5] Recently; ZFHX1B mutations have been detected and also a 19qter deletion was showed in a patient.[6]

Light microscopy of the biopsy obtained from the hyperpigmented skin revealed high degree of pigmentation up to the upper epidermal layers, while the electron microscopy showed several melanosome abnormalities such as increased number and abnormal maturation.[7,8] Chromosome studies from fibroblast cultures usually show normal karyotypes.[2,3,7,9] However, chromosomal mosaicism in fibroblast cultures is also possible.[2,10,11]

Cutis tricolor is associated with multisystem birth defects such as craniofacial anomalies including hypertelorism, epicantal folds, wide philtrum, backward rotated ears, brushy eyebrows, deep nasal bridge with broad nostrils, mental and motor retardation, epileptic seizures, a behavioural phenotype, severe kyphoscoliosis and non-specific brain abnormalities.[2,3,6] We have defined most of these craniofacial anomalies and brain abnormalities with developmental delay in the present case; however, she had no epileptic seizures. Also, oligodendroglioma, ataxia-telangiectasia and phacomatosis pigmentovascularis and cataract with cutis tricolor were reported.[5,12-14]

Brain is the most affected organ in cutis tricolor because developmental delay, epilepsy and mental retardation are common in reported cases. In only one report, brain MRI scans revealed multiple, diffuse, nonspesific, subcortical and periventricular lesions.[9] The present case was diagnosed with cutis tricolor parvimaculata with clinical and radiological findings. The skin lesions of this patient were reminiscent of a pigmentation disorder reported by Larralde and Happle.[5] In their report oligodendroglioma was also determined. The MRI findings of our patient revealed subcortical and periventricular mass lesions. The lesions did not resemble abcess, tuberculomas or the tumours and unidentified bright objects described in neurofibromatosis or tubers associated with tuberous sclerosis.[15-17] Besides, the lesions were hypovascular in perfusion MRI and diffusion was normal in diffusion MRI while choline and lipid peaks were detected in proton magnetic resonance spectroscopy. So far, the lesions in the present case differ from these described lesions by its subcortical and periventricular localization; size, greater than tubers or unidentified bright objects; and limits, slightly restricted. It is possible for tumours to develop on the basis of these unknown lesions. Cho/Cr ratio suggested tumoral growth. Thus, during the follow up period, enlargement of these unknown lesions in our patient supports this view. We suggest that these lesions may be the typical findings of cutis tricolor in early life. To the best of our knowledge, the perfusion, diffusion and MR spectroscopic findings of brain lesions have not been reported. It is interesting that there were no acute clinical manifestations in spite of the various large sized multiple lesions. Until now, a comprehensive inventory of brain involvement associated with cutis tricolor has not been available because the number of case reports is so far limited and all cases were in advanced ages. Overall, to support our suggestion new case reports and pathological analyses are needed.

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