Aplasia cutis congenita (ACC) is a rare developmental malformation characterized by the absence of skin, and often extends to bone or dura in a localized or widespread area at birth. ACC is seen most commonly on the scalp reported up to eighty-four percent of all cases in the literature. It often manifested as a solitary lesion without other anomalies, but sometimes represented as part of a heterogeneous group of disorders. We presented a case of ACC associated with cutis marmorata telangiectatica congenita, secundum atrial septal defect and epilepsy which seem not fit well with any previously recognized clinical syndrome. In addition, emphasis on pathogenesis, histopathology, and treatment strategies were also discussed. (Dermatol Sinica 26: 157-164, 2008)

Key words: Aplasia cutis congenita, Cutis marmorata telangiectatica congenita, Atrial septal defect, Epilepsy

INTRODUCTION

Aplasia cutis congenita (ACC) was first described by Cordon in 1767, and there were more than 500 cases reported around the world with a slight female preponderance. It refers to a congenital focal defect of skin present at birth which can be found at any part of the body surface, but predominantly at vertex of cranium. ACC can occur sporadically or as part of heterogeneous disorders. Several other associated disorders were reported such as anomalies of the eyes, ear-nose-neck, skin and so on. In addition, some clinical syndrome also included manifestation of ACC such as Adams-Oliver syndrome, Wolf-Hirschhorn syndrome, Trisomy 13 (Patau syndrome) and other rare clinical syndrome. We reported a patient who had manifestations characterized by ACC, cutis marmorata telangiectatica congenita (CMTC), secundum atrial septal defect, and intractable epilepsy which has been not reported in the literature.

CASE REPORT

A 1-year-old male infant suffered from epilepsy for about one month characterized by clonic seizures of bilateral limbs altern-
respectively, simultaneously with upward slanting eyes and loss of consciousness at a frequency of three to eight fits per day. He had been treated at many local hospitals, but intractable seizure remained. So, he was brought to our pediatric department for further evaluation. At admission, dermatologic service was consulted at the same time due to peculiar cutaneous findings on both scalp and trunk.

The patient was delivered at term by Cesarean section in Canada. The mother had suffered from one episode of vaginal bleeding at the end of first trimester. However, there was no significant abnormality observed by the obstetrician. In addition, there was no history of maternal abuse of alcohol, smoking, or drugs, nor of intrauterine infections. No history of birth trauma, injury from forceps, amniocentesis, or other iatrogenic cause was noted. Family history was unremarkable. At birth, he was found to have scalp defects which were characterized by two well-demarcated, erythematous, superficially eroded skin lesions measured 2 cm and 1.5 cm in diameter respectively located on the vertex of the scalp (Fig. 1, taken at birth). In addition, extensive reticulated mottled erythematous patches were also found on the trunk. However, the scalp lesions were treated with topical antibiotics and gradually healed within the first few months. The mottled lesion along with few scaling plaques of both bilateral elbows and back was firstly diagnosed as ‘atopic dermatitis’ and was treated with topical corticosteroids. Erythematous and reticulated lesions on the torso showed gradual improvement over time. The physical and neurological examinations at birth were normal, and cardiologic examination disclosed a secundum atrial septal defect under the echocardiography.

During hospitalization, physical examination and image surveys were done. On admission, the patient was ill-looking with relatively well activity. Delayed development was noted by inability to pull to stand and walk with help or alone. Neurological examination showed increased deep tendon reflexes of bilateral limbs, and the Babinski signs were absent. A systolic ejection murmur at second left intercostal space and fixed split of second heart sound were noted, which was later diagnosed as secundum atrial septal defect with echocardiography. Cutaneous examination disclosed two well-defined, indurated, skin-colored, hairless plaques,
3.5 cm and 2.5 cm in diameter respectively, over the vertex of scalp (Fig. 2, taken at 12 months old). Another finding was the barely visible reticulated brownish mottled variable-sized patches on the skin of the trunk (Fig. 3). The latter findings were compatible with the clinical diagnosis of CMTC. Other physical examinations were unremarkable. Laboratory examinations including complete blood count, biochemistry and urine analysis were all within normal limits. Computed tomography of the brain demonstrated two small skull defects over the vertex at the level compatible with the overlying skin lesions (Fig. 4). Together with the scalp skin lesions, ACC was diagnosed clinically. No intracranial lesions were noted. Regional positron emission tomography showed hypometabolism over the left-sided temporal lobe and bilateral parietal lobes. Electroencephalogram (EEG) revealed multifocal paroxysmal disorder, more prominent at right frontal and parietal area which was an essentially abnormal sleep EEG for the age of the patient.

The patient was treated with oral levetiracetam, supplemented with vitamin B6 for epilepsy control. Skin lesions of both ACC of the scalp and CMTC of the trunk were managed conservatively by observation.

**DISCUSSION**

ACC is an unusual congenital malformation of the skin, and is most often a benign isolated defect. However, it can be associated with other physical anomalies or as part of malformation syndromes. The lesions of ACC varied considerably. It could be linear, round, oval, stellate, or even punched-out in shape. In addition, lesions may manifest as superficially eroded, deeply ulcerated, completely scarred lesion or covered with a membranous epithelium filled with serous fluid resembling a blister. Hypertrichosis of the adjacent scalp had been reported. Besides, about one-fourth of patients had associated involvement of underlying cranial bones and dura matter and they underwent spontaneous resolution during infancy. The areas in which ACC involved were mostly limited to one region of the body surface, but sometimes they can scatter over the trunk and extremities. Systemic ACC was extremely rare, and there are only two cases reported so far. The diagnosis of ACC is established mainly on clinical ground. Our case had superficially eroded skin defect with underlying bony defect.

Most cases of ACC have not been studied histologically. However, some cases undergoing skin biopsy showed inconsistent results when lesions evolved with age. At birth, the lesion may involve only the epidermis and upper dermis, but ulcerated lesions may demonstrate complete absence of all layers of skin, exposing the subcutaneous fat, and occasionally extending to the bone or dura. Healed areas often show, besides a flattened epidermis, proliferation of fibroblasts in a loose connective tissue stroma, newly formed capillaries, and complete absence of adnexal structures.

The pathogenesis of ACC was not completely understood, and several hypotheses had been proposed. Some authors suggested that ACC may be correlated with neu-
Mallory and colleagues had proposed that either vessel abnormality or a vascular infarct can lead to degeneration of the involved skin. Padget considered incomplete healing and fusion of the mesoderm in patients with ACC, because a healthy mesoderm is essential for the development and continued subsistence of the ectoderm. Ischemic or thrombotic events may be responsible for cases of placental infaction or fetus papyraceus. Furthermore, certain instances of ACC are probably related to an underlying involuted leptomeningeal angioma or even sinus pericranii. A few case reports are linked to certain teratogens. Methimazole, an antithyroid agent, are among the causative agents for ACC. Other medications suspected to relate to scalp or cranial defects are misoprostol, cocaine, aminopterin/methotrexate, captopril, enalapril and benzodiazepines. These medications should be avoided in young sexually active women. Intrauterine infection had also been correlated with the occurrence of ACC, such as herpes simplex infection and varicella infection.

Genetic factors play an important role in the development of ACC, either chromosomal abnormalities or monogenic inheritance expressed as autosomal dominant, autosomal recessive, and X-chromosomal inherited syndromes was identified. For instance, Patau syndrome, also known as trisomy 13, is a disorder of chromosomal abnormality that manifests ACC on more than fifty percent of affected patients. Adams-Oliver syndrome is a disorder characterized by ACC with terminal transverse limb defects and is most often inherited in an autosomal dominant pattern, but rare cases of autosomal recessive inheritance had been reported. Johanson-Bizzard syndrome (JBS), which was autosomal recessively inherited, had features of scalp ACC and other important features such as nasal alar hypoplasia, dental anomalies, pancreatic insufficiency and congenital deafness. Zenker et al. detected mutations in the gene UBR1 by high-throughput direct sequencing of DNA from individuals with JBS. These examples gave rise to a hint that genetic abnormalities attributed to at least some cases of ACC.

CMTC, first described in 1922, is an uncommon cutaneous disorder characterized by a localized or generalized reticulated, vascular, blue-violet network of the skin. Skin lesions are usually present at birth and show a marked improvement over time. It had been considered a vascular disease originating from the defects of mesodermal system during embryonic life, but some authors thought that the cause may be multifactorial. Diagnosis of CMTC is mainly clinical. CMTC are frequently reported to be associated with other congenital anomalies such as body asymmetry, vascular, neurologic anomalies, glaucoma, transverse limb defects, ACC and even mental and psychomotor retardation. Sometimes, cutaneous atrophy or ulcerations of the skin may be observed in the affected individuals. Rarely associated
anomalies of CMTC include patent ductus arteriosus, congenital generalized fibromatosis, syndactyly, neonatal ascites, multicystic renal disease and so on. The prognosis of CMTC is usually fairly well if there is no associated fatal congenital anomaly. Our case had rare combination of CMTC with ACC, seizure and secundum atrial septal defect which was seemed not to be reported before. However, skin lesions improved gradually over time and there was no associated fatal congenital malformation in our patient. A good prognosis of our case can be expected.

In 1986, Frieden analyzed 120 publica-

Table. 1 Frieden’s Classification of Aplasia Cutis Congenita (ACC)

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>Scalp ACC without multiple anomalies</td>
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<tr>
<td>2</td>
<td>Scalp ACC with associated limb anomalies (limb reduction anomalies, 2-3 syndactyly, club-foot, nail absence or dystrophy, skin tags on toes, persistent cutis marmorata, encephalocele, woolly hair, hemangioma etc.)</td>
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<tr>
<td>3</td>
<td>Scalp ACC with associated epidermal and organoid nevi (corneal opacity, scleral dermoids, eyelid colobomas, psychomotor retardation, seizures)</td>
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<td>4</td>
<td>ACC overlying embryologic malformations (meningomyeloceles, spinal dysraphism, cranial stenosis, congenital midline porencephaly, leptomeningeal angiomatosis, ectopia of ear, omphalocele, gastroschisis)</td>
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<td>5</td>
<td>ACC with associated fetus papyraceus or placental infarcts (these cases showed extensive truncal and limb involvement, usually symmetric and frequently with linear and stellate areas of aplasia)</td>
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<tr>
<td>6</td>
<td>ACC associated with epidermolysis bullosa (Blistering of skin and/or mucous membranes, absent or deformed nails, metatarsus varus, congenital absence of kidney)</td>
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<tr>
<td>7</td>
<td>ACC localized to extremities without blistering</td>
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<tr>
<td>8</td>
<td>ACC caused by specific teratogens (maternal exposure of methimazole or carbimazole, signs of intrauterine infection with varicella and herpes simplex infections)</td>
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<tr>
<td>9</td>
<td>ACC associated with malformation syndromes (trisomy 13, 4p- syndrome, many ectodermal dysplasias, Johanson-Blizzard syndrome, focal dermal hypoplasia, amniotic band disruption complex, XY gonadal dysgenesis)</td>
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tions from 1917 to 1985 and proposed classification of ACC into nine groups (Table 1) which were currently the most often used one. The classification was based on the location, pattern of ACC, associated abnormalities, and mode of inheritance. Our case presented as skin defect of the vertex of the scalp, associated with CMTC, secundum atrial septal defect, epilepsy, and occurred as a sporadic case without family history. In Frieden’s classification, our case may be classified as group 1 which is scalp ACC without multiple anomalies. However, in this group of ACC, several isolated abnormalities have been reported associated with vertex defects such as mental retardation, patent ductus arteriosus, heart disease, omphalocele, polycystic kidneys, double cervix and uterus, and cutis marmorata telangiectatica congenita. Our case had associated abnormalities of atrial septal defect and seizure which were not previously reported in this group. Seizure was only described as an abnormal association with ACC in group 3. Nonetheless, this category constitutes cases mainly associated with epidermal and organoid nevi which was not present in our case. Therefore, it is difficult to put our case to either of the nine groups of ACC. Our case presents a combination of separate clinical entities, may be a variant of certain malformation syndrome or a newly recognized syndrome. More investigations and continued clinical observation are needed in order to clarify and understand the nature and etiopathogenesis of our patient.

Treatment strategies are tailored according to the size and presence of underlying bony defects of the lesion. Most lesions on the scalp can be managed with routine wound care and heal spontaneously within weeks to months after birth. Large lesions with an underlying skull defect require surgical closure to prevent massive hemorrhage and infection. When it is difficult for primary closure, a plastic repair with full thickness vascularized pedicle graft can be utilized. Large skull defect may require reconstruction by bone graft.

In conclusion, when a clinician managed a patient with ACC, an effort to a thorough history taking, physical examination, image surveys and even genetics study should be made to rule out any other associated anomalies.

REFERENCES
先天性皮膚發育不良症，合併先天性微血管擴張性大理石狀皮斑，心房間隔缺損及癲癇：
一個新的臨床症候群？

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先天性皮膚發育不良症是一種罕見的先天性發育異常，臨床上可見在出生時，有局限性或廣泛性的皮膚缺損，且常常深達骨組織或是軟腦膜。病灶最常出現在頭皮上，在文獻報導中，有高達百分之八十四的病患是在頭皮上。它可能單獨存在並未伴隨著其它的先天性異常，也可能是一些異質性疾病的一部分臨床表現。我們在本篇報告一位先天性皮膚發育不良症的病患，同時合併先天性微血管擴張性大理石狀皮斑、心房間隔缺損及癲癇。本案例似乎不符合任何已知的臨床症候群。此外，我們也討論了關於先天性皮膚發育不良症的致病機轉，組織病理學及治療對策。（中華皮誌：26: 157-164, 2008）