APLASIA CUTIS CONGENITA CURRENT VIEWS AND A CASE REPORT

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INTRODUCTION :

Aplasia cutis congenita (ACC) describes localized or widespread areas of absent skin. The defect occurs in utero and is seen at birth. Lesions occuring in early gestation may heal before delivery and appear as areas of atrophy, fibrosis, scar-like or alopecia[1]. Unhealed lesions appear as ulceration with granulation tissue and sometimes extend to subcutis, bone or dura[2]. ACC is a rare disorder and the number of reported cases from many part of the world since its original description in 1767 is more than 500[2]. ACC affects males and females equally and may have a sporadic or familial incidence.

Case Report :

L.A. is a female from Qatar - born full term normal delivery and appropriate for her gestational age and weighed 3.2 Kg on 17.11.1994. She was admitted to the Paediatric Intensive Care Unit immediately after birth for ulceration of her skin. The infant was well with normal vital signs and no dysmorphic features. She had well demarkated granulated reddish ulcerations on chest wall, both upper limbs, both knees and chins (Fig. 1,2,3,4). Mucous membranes were not affected and no bullae were seen. Scalp, face, hands and feet were free.

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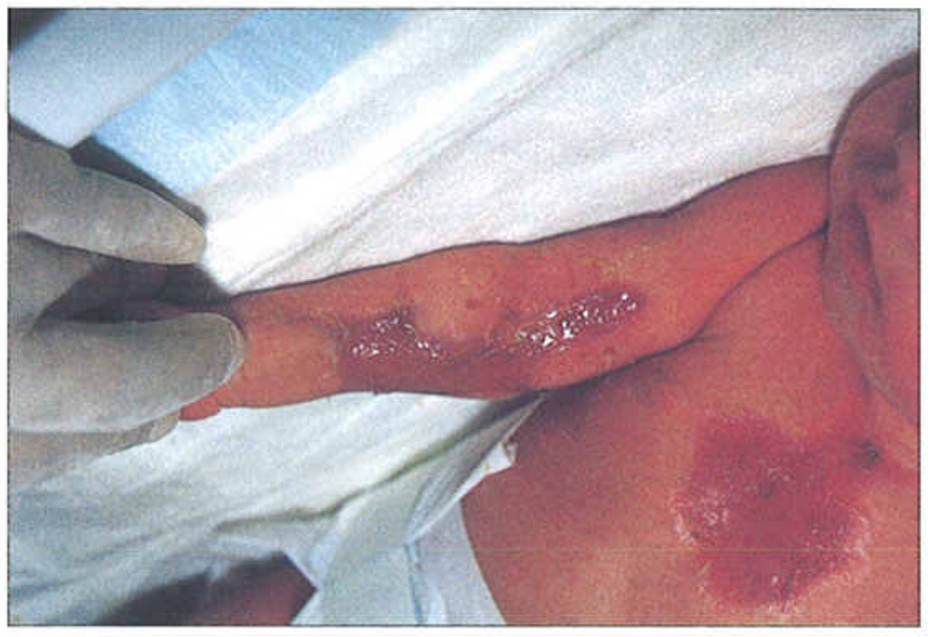

Fig 1: ACC affecting chest wall and right upper limb

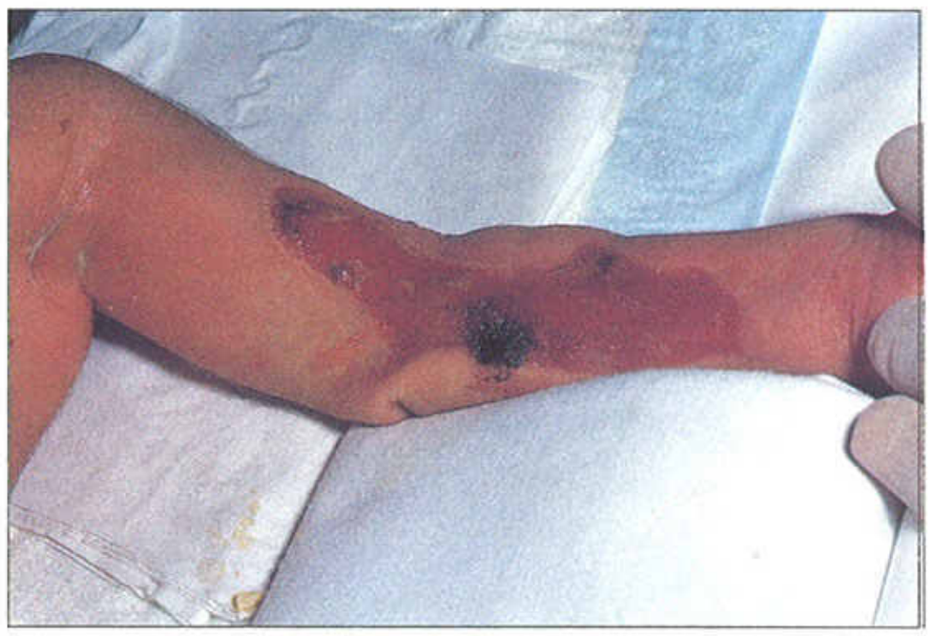

Fig 2: ACC affecting left upper limb

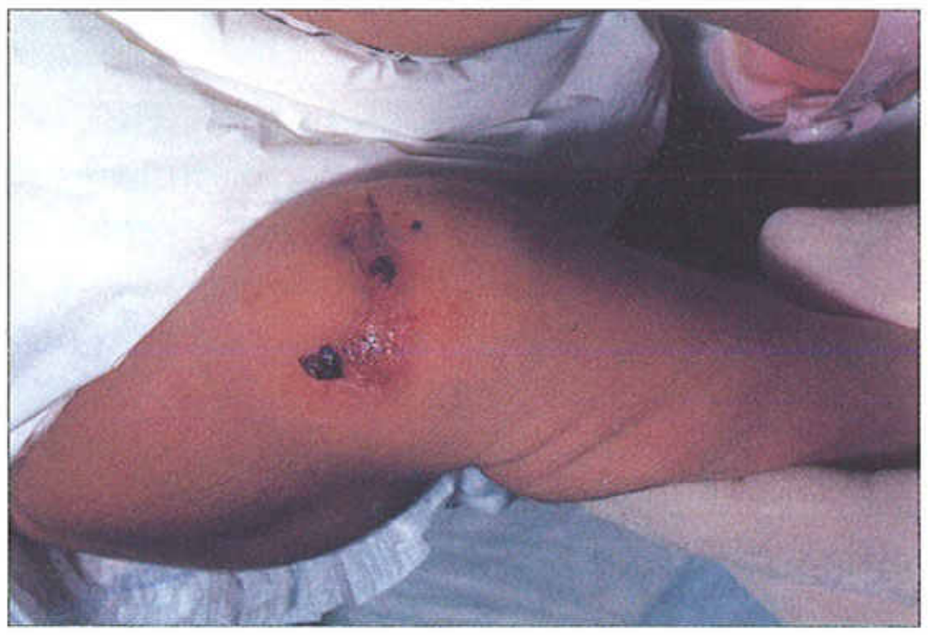

Fig 3: ACC affecting right knee region

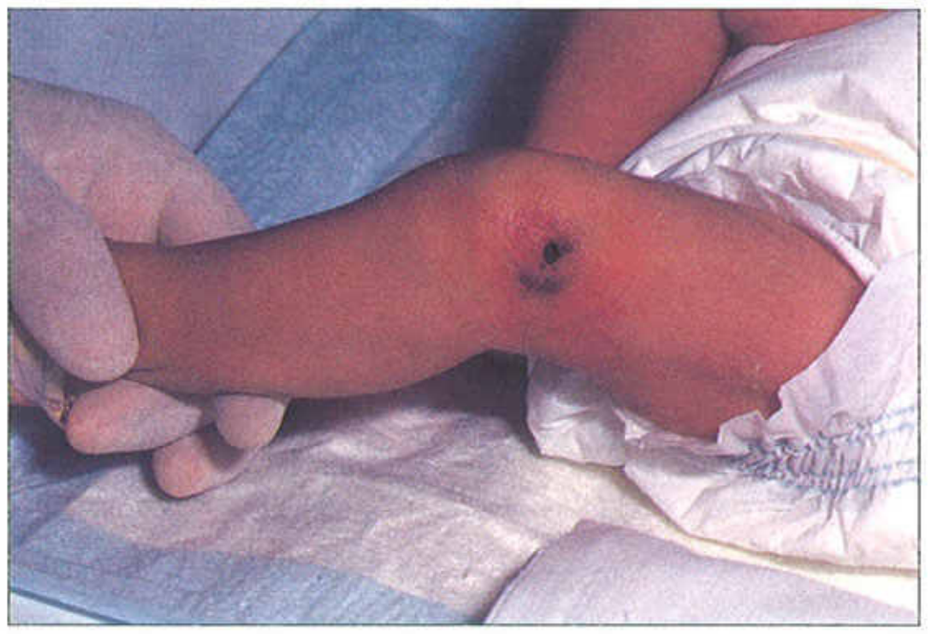

Fig 4: ACC affecting left knee

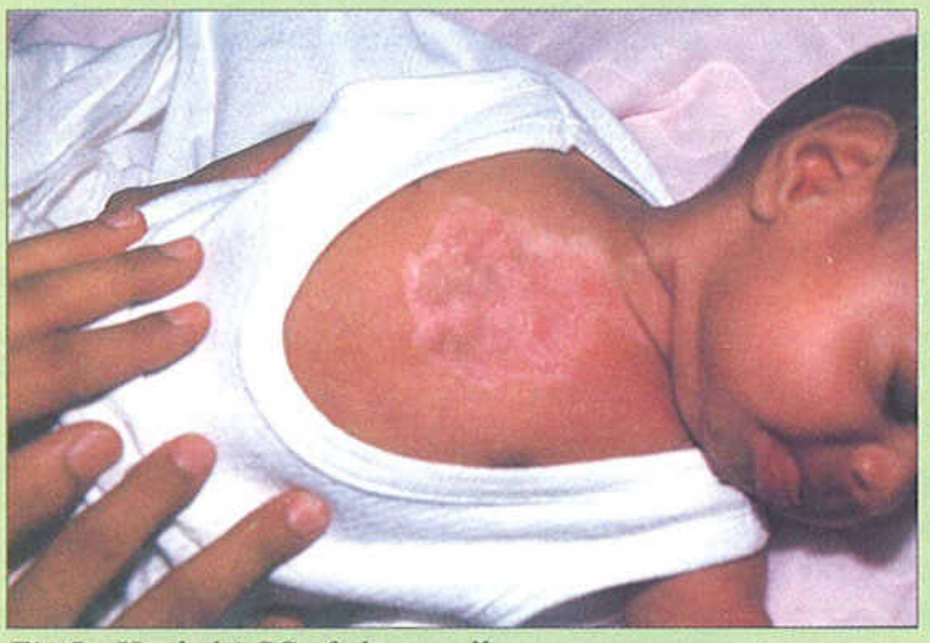

Fig 5: Healed ACC of chest wall

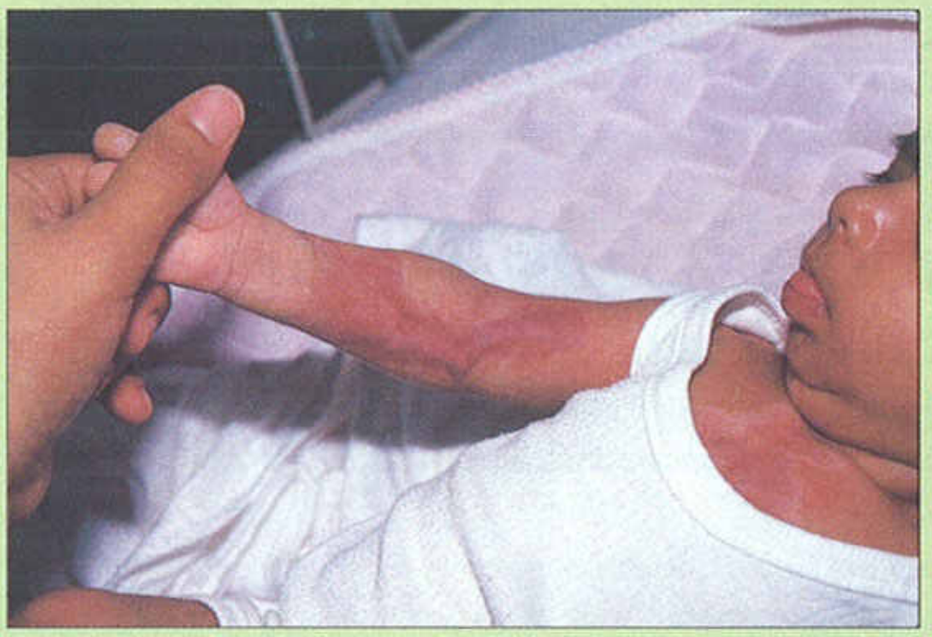

Fig 6: Healed ACC of right upper limb

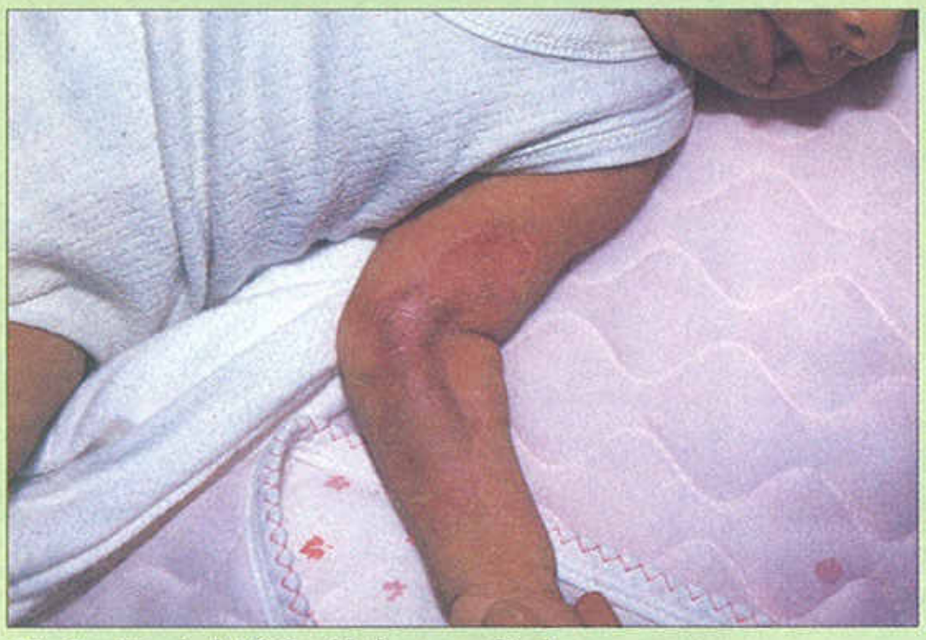

Fig 7: Healed ACC of left upper limb

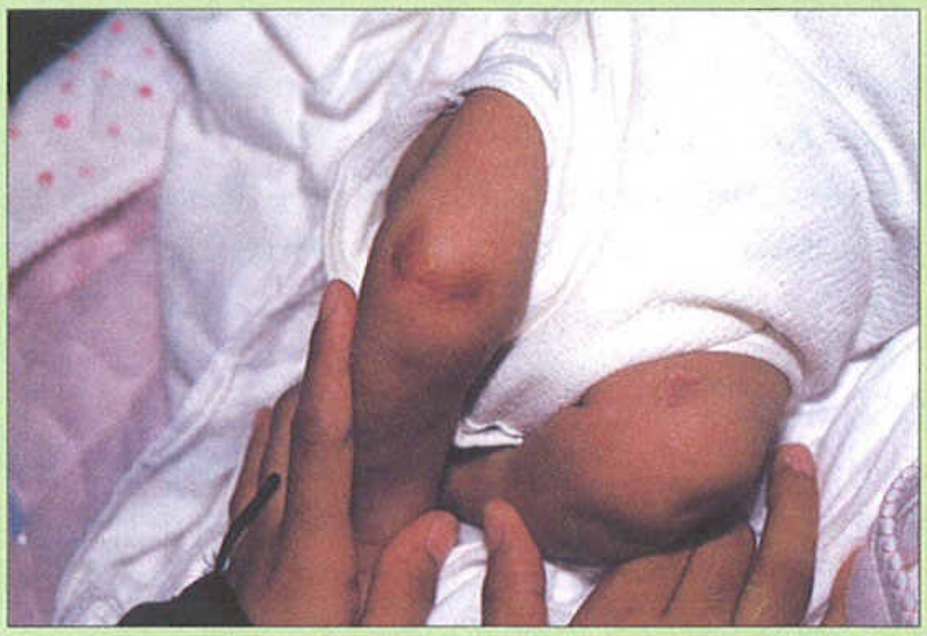

Fig 8: Healed ACC of both knees

Investigations done included CBC, serum electrolytes, blood biochemistry, immunoglobulin estimation, skull X-ray and ultrasonography of the brain and abdomen all results were normal. Cytogenetic study showed a normal female karyotype 46 xx and no chromosomal abnormality was detected. Skin biopsy from the lesion of the right arm was taken for light and electron microscopic examinations. The infant had four healthy sisters, her mother did not suffer from any infections or take any drugs during her pregnancy. The family history was negative for similar conditions. Infant was diagnosed to have aplasia cutis congenita. The lesions were treated with Soframycin dressing and all the defects healed within three months leaving atrophic scars. (Fig. 5,6,7,8).

Pathology : (Fig 9,10,11,12)

Section (H/8122/94) of the skin biopsy show an area of necrosis affecting full thickness of the epidermis including basal layer (Fig 9, 10 & 11.) This has resulted in ulceration with destruction of the basement membrane which cannot be seen in the ulcer base even in the section stained with PAS. Basement membrane in normal skin adjacent to the ulcer appears quiet thin. Granulation tissue is present in the dermis with fibroblasts and capillaries arranged perpendicular to the skin surface (Fig 12). Thickness of the epidermis and organization of dermal connective tissue adjacent to the ulcer appear normal, although basement membrane appears quite thin. Hair follicles are present in the biopsy (Fig 9). Electron microscopic examination of the skin sample shows no evidence of separation of epidermis from dermis. Some degree of spongiosis is evident. Keratin tonofilaments are normal with no signs of bullous formatin or clumping. The hemidesmosomes are normal and well formed with well defined sub basal plates. Anchoring fibrils are present but may be fewer than normal in areas where there has been re-epithelialization. There was no splitting of the basement membrane zone which appeared normal.

Clinical Aspects :

ACC may affect any part of the skin of neonate. The lesions may be superficial or deep and vary in size from 0.5 to 100 cm[1]. ACC is most often solitary in 74.9% and multiple in 25.1% of the patients. Lesions found on the trunk are single in 6.9% and multiple in 11.4% of all reported cases. Most defects occur on the head where lesions are single in 86% and multiple in 43%[3]. It is reported that 20-30% of ACC of the scalp show bony defects[4] and it is estimated that underlying bone lesion is seen in 10% of all ACC[5]. Bone defects seen are never found without skin involvement and the defect in the bone is never greater than the area of affected skin and the most common affected part of the skull is the vertex[6]. ACC of the scalp may be associated with alteration of the shape of external ear becomming cupped or folded and stood out from the head with aplasia or hypoplasia of nipple[7].

ACC of the scalp may be membranous and has a thin glistening parchment like covering with round or oval configurations and sharply delineated border. The membraneous aplasia cutis arises during early fetal development and appear in the perinatal period as soft translucent cyst and tend to be punched out with friable raw base that heals with scarring and may be encircled with hypertrophic hairs known as the hair collar sign[8].

Hypertrophic hairs are also seen in congenital and acquired pigmented nevi, neurofibromas, spinal dysraphism and sympathetic dystrophy[4]. Hypertrophic hairs are known to mark the exit of intracranial dermal sinuses as well as spinal sinuses. (Faun Tail).

Membranous scalp lesions in six neonates were reported to display the hair collar sign[4]. Such lesions have to be differentiated from forms of cranial neural tube defects as encephalocele, meningococele, cutaneous ectopic psammoma and heterotopic brain tissue (HBT) whch is cerebral tissue found in skin without underlying defect of the cranium[8]. HBT may arise from a pinched off ectoderm which differentiates into a neural structure or HBT may result from overgrowth of neural tube that becomes isolated by subsequent restoration of the integrity of the cranium[8].

All these lesions appear on occipital or parietal scalp of neonate. They appear clinically as bald lesions 2-4 cm on the scalp. They may be cystic or solid, reddish blue or skin coloured and show the hair collar sign, which is considered a marker of cranial tube defect[8].

Clinicians should be alerted to investigate and define any congenital bald lesion of the scalp with ultrasound, cranial tomography and surgical consultation before any form of intervention is done in order to exclude any connection with the underlying nervous tissue.

Multiple anomalies were reported in associtation with ACC such as cleft palate, cleft lip, tracheo-oesophageal fistula, intestinal lymphangiectasis, double cervix, double uterus, cutis marmorata

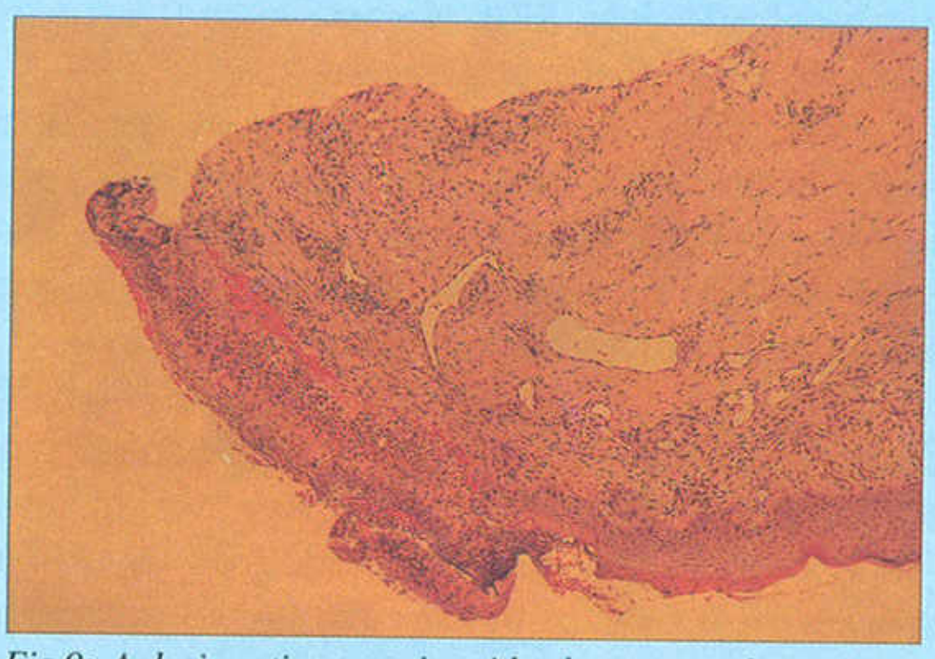

Fig 9: Aplasia cutis congenita with a large area of ulceration. Hair follicles are present in the biopsy (HE x 5).

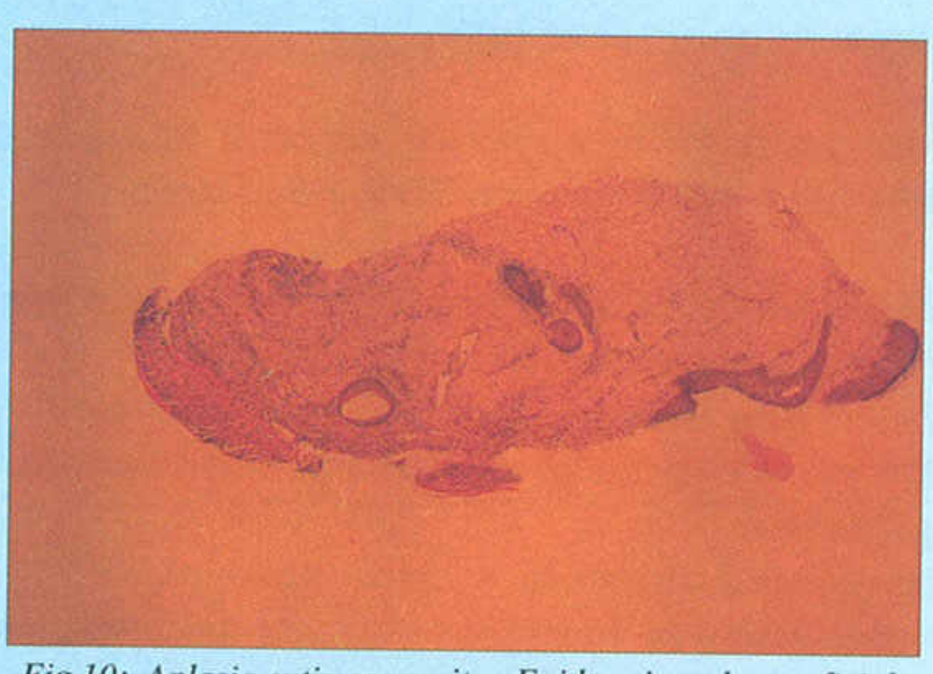

Fig 10: Aplasia cutis congenita. Epidermis and superficial papillary dermis has been destroyed in the ulcer zone. Ulcer bed is covered by acute inflammatory exudate. Note granulation tissue with prominent vessels in the dermis (HE x 10).

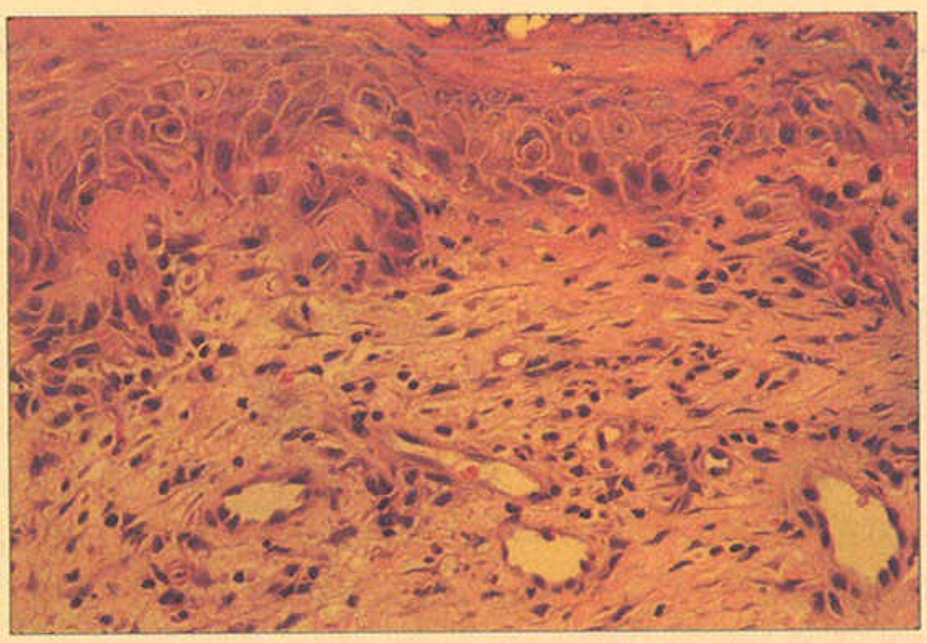

Fig 11: Aplasia cutis congenita. Fibroblastic proliferation and vascular spaces are seen in granulation tissue in the dermis (HE x40).

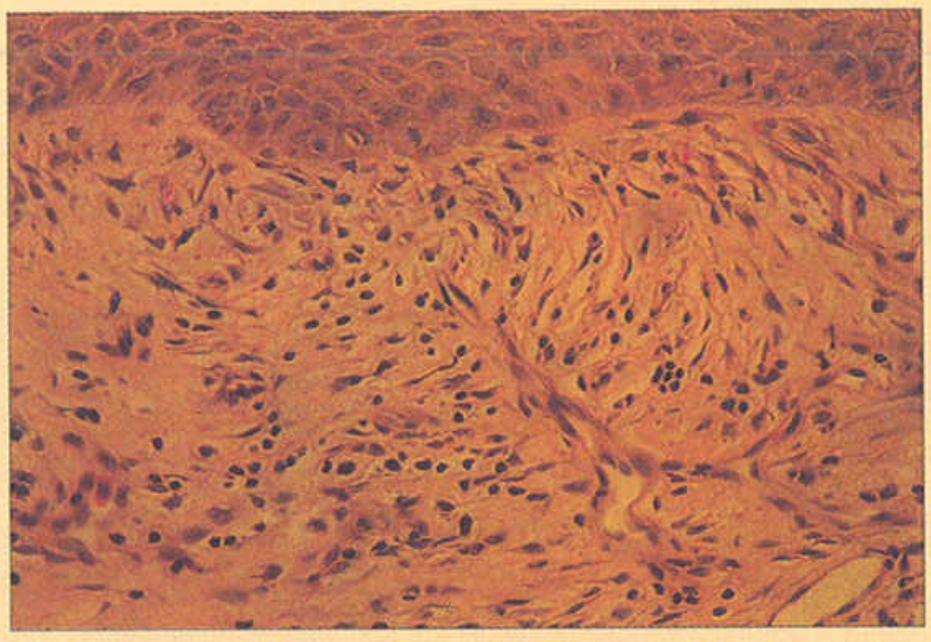

Fig 12: Aplasia cutis congenita. Proliferating fibroblasts in the dermis are oriented somewhat perpendicular to the skin surface (HE x 40).

telangiectatica congenita, syndactyly, hypoplasia of distal phalanges of hands, ectrodactyly of the feet, shortened right foot with talipes equinovarus (Adams Oliver Syndrome), epidermolysis bullosa of lower limbs and trunk, middle phalangeal reduction, distal limb absence, congenital dysfunction of major peripheral nerves in congenital constriction band syndrome with ACC, epidermal nevus, Fallot's tetralogy and dextrocardia[2,6,7,9,10,11,12,13].

ACC heals within weeks or months and healing occurs from periphery to center[13]. Superficial lesions heal with minimal scarring and hair loss. Lesions treated using silver sulfadiazine cream dressing may not heal and such conservative treatment may be complicated by infection or fatal haemorrhage. Large lesions may need grafting especially with an underlying cranial defect in order to protect the dura and prevent meningitis. Such defect could be closed by two rotational scalp flaps (Orticochea technique) at birth[15].

Haemorrhage from superior sagittal sinus and meningitis have been fatal in 20% of cases[16].

The dignosis of ACC depends on its clinical presentation and has to be differentiated from[17]:

1) Ulceration induced by fetal scalp electrode
2) Obstetric trauma from forceps and vacuum extraction
3) Congenital alopecia without scarring
4) Volkmann's ischaemic contracture characterized by forearm wound, motor and sensory loss of hands, forearms followed by muscle retraction[18].
5) Cranial neural tube defects.

In a review of 331 cases of ACC only 48 had histologic examination[3]. The histologic appearance is variable. The epidermis, dermis, subcutis and even deeper tissues may be absent. In scarred lesions the epidermis is thin and covers sclerotic cicatrix. Appendages are absent or rudimental and sometimes rest of glial cells are present[17,19,8].

Friedman[2] in his review of ACC proposed a classification based on:

1) Characteristic location
2) Charcteristic pattern of skin defect
3) Associated malformations
4) Mode of inheritence

Nine clinical groups were proposed (Table 1) and include:

Type I. Congenital absence of the skin on the scalp without multiple anomalies: autosomal dominant inheritance and chromosomal abnormalities may be a predominant factor.

Type II. Congenital absence of the skin on the scalp with limb reduction abnormality, autosomal dominant inheritance and sometimes recessive.

Type III. Congenital absence of the skin on the scalp with epidermal and organoid nevi.

Type IV. Congenital absence of the skin overylying developmental embryologic malformations.

Type V. Congenital absence of the skin associated with fetus, papyraceus characterized by delivery of a dead twin (in utero death of a twin during second trimester is described as fetus papyraceus).

Type VI. Congenital absence of the skin as feature of apidermolysis bullosa (EB); ACC occurs in associatin with EB simplex (dominant), junctional EB and dystrophic EB (dominant and recessive subtypes).

Type VII. ACC localized to the extrimities without blistering; inheritance is autosomal dominant or autosomal recessive or sporadic, especilay in placental infarction and fetus papyraceus.

Type VIII. ACC caused by specific teratogenic agents

Type IX. Congenital absence of the skin as a manifestation of malformation syndromes.

1) Trisomy 13 (D1 Trisomy).
2) Deletion of short arm of chromosome 4 (4-P syndrome).
3) Occulo-cerebro-cutaneous syndrome
4) Johnson-Blizzard syndrome
5) Focal dermal hypoplasia (Goltz' syn drome)
6) Bitemporal ACC
7) Focal facial dermal dysplasia

Aetiology :

The causes of ACC include genetic factors, teratogens, compromised vasculature and trauma[17].

The skin and nervous system both originate from ectoderm. The neural ectoderm separates from epithelial ectoderm at the time of closure of neural tube. A number of factors have been identified to predispose to neural tube defects. These factors include maternal diabetes mellitus, maternal heart or lung diseases, the use of diuretics, antihistamines and sulfonamides during pregnancy[8].

The underlying cause or causes of ACC are mere speculations.

It is suggested that membranous ACC is a form frust of a neural tube defect and may be derived from a similar embryogenic defect[4].

It has also been suggested that ACC could be an amnion rupture malformation sequence. It is estimated that only 1 in 2000 demonstrate clinical malformation reflecting amnion rupture such as constricting bands, club foot, anencephaly, encephalomeningococele and cleft lip and palate. After amnion rupture, the amniotic sac stops to develop leading to oligohydramnios which may cause adherence of fetal skin to chorion, thus tearing the skin and leaving an area of aplasia cutis[3].

Intrauterine trauma was suggested as a cause of ACC but a minotiry of cases gave history of intrauterine trauma.

ACC is in part genetically determined. In a family, 12 members over five generations were reported to have ACC, a finding that supports an autosomal dominant inheritance[20]. Several families with dominantly inherited ACC with wide variation in expression have been described[5,13,21].

One third of patients with trisomy 13 have scalp ACC and may have elevated alfa feto protein (AFP) which is a marker of neural tube defects where amniotic fluid levels of AFP are increased because of contamination with CSF[4]. Some authors suggest that all scalp ACC with underlying cranium defect is pathgenetically related to encephalocele[22]. Somatic mosaicism was suggested as the most probably cause of ACC which had a distribution reminiscent of lines of Blaschko[16].

ACC in twin pregnancy with fetus papyraceus appears to be related to fetal demise in the late first or early second trimester when disseminated intra vascular coagulation may cause selective hypoperfusion of mesodermal tissue of the skin producing full thickness loss of skin and subcutaneous structures[23]. Increased risk fo ACC should be considered when during prgenancy there is elevated maternal AFP and elevated amniotic AFP with a distinct electrophoretic band of acetylcolinesterase especially in twin pregnancy with fetus papyraceus[24]. A mother who had increased AFP in the serum in midtrimester with elevated amniotic acetylecholinesteras band delivered a premature baby with ACC[25]. It is postulated that the change in the concentration of acetylecholinesterase in amniotic fluid was probably secondary to healing in the exposed nerves of ACC[24]. AFP, skin biopsy and ultrasonography have been used for prenatal diagnosis of ACC[26].

Elevated amniotic fluid AFP with a positive cetylecholinesterase band was first described by Cruickshank and Grandos in a fetus with ACC[27]. Conditions reported to be associated with a positive acetylecholinesterase band include open neural tube

defects, ventral wall defects, fetal death in utero, oesophageal atresia, cystic hydroma, teratomas and ACC[28].

It seems that vascular malformations of the skin could play a role in development of ACC[29]. Acrania which is a rare anomaly in which there is absence of flat bones, of cranial vault is always associated with severe form of ACC. So, acrania is a severe form of ACC which may be due to disruption of developing blood vessels with selective effect on membranous neurocraneum or may be related to severe fetal hypotension[6]. ACC relates to changes that occur before the early second trimester. Episodes of hypotension or disseminated intravascular coagulation may cause selective hypoperfusion of mesodermal tissue and skin of the trunk[23]. An underlying vascular cause for ACC has been emphasized[2]. The anatomic characteristics of ACC in twin of fetus papyraceus may be related to the vascular plexus that supplies the fetal skin. This vascular plexus is part of segmental blood vessels especialy intercostals. In the thoracic area these perforating vessels extend from intercostal arteries and are well developed by 17-20 weeks gestation. Intercostal arteries may get affected leading to ACC in the region perfused by these vessels[23].

Teratogenic agents were also proposed to be aetiological in ACC. Calvarial hypoplasia was found in associtions with intrauterine exposure to angiotensin converting enzyme inhibitor[6]. ACC was reported in an infant whose motehr was treated with valproic acid during pregnancy. Valproic acid is known to increase the risk of spina bifida and other midline defects. ACC is regarded as a cutaneous marker of neural dysraphism[30]. Antithyroid drugs used during pregnancy for the treatment of hyperthyroidism was reported to be associated with ACC especially the thioamide methiamazole. However, there is insufficient evidence either to establish or eliminate a direct causal relationship between ACC and methiamazole use[31].

Intrauterine herpes varicella zoster infection may cause ACC of the scalp, microcephaly, chorioretinitis, skin vesicles, skin scarring and ACC of the neck, shoulders and legs[2].

ACC was reported in association with neonatal L E[32].

Tension induced disruption of the skin of scalp during rapid brain growth between 10th and 18th week of gestation was suspected to be aetiolgoical in scalp vertex ACC[33].

Discussion :

In this report we described a case of ACC whose family history is negative for similar defect. The infant's mother was not exposed during pregnancy to trauma, infection, or teratogenic factors. According to the clinical data found this case is likely to come under Group V according to Freiden[2] classification although there was no infant papyraceous or placental infarction. The infant had no other deformities or chromosomal abnormality. All lesions healed spontaneously within 3 months and there was no clinical evidence of epidermolysis bullosa at birth and during a follow up period of 18 months.

Ultrastructural studies in our case have confirmed the diagnosis of aplasia cutis congenita and excluded any possibility of epidermolysis bullosa. However, a similar pathology may be seen in mildly affected children with the recently described laryngo-onycho-cutaneous syndrome which so far has been confined to Pakistani ethnic group (Phillips et al, 1994)[34]. The clinical picture is quite distinctive in the three children with this syndrome who developed hoarse voice within two weeks of birth. All had developed laryngeal abnormalities, chronic skin ulceration, nail dystrophy, and conjunctival disease in infancy. In every case, dental enamel was hypoplastic and both skin and mucosal surfaces demonstrated increased susceptibility to trauma. Progression of disease occurred, to life threatening respiratory obstruction in the third child. Ultrastructural and immunohistological examinations showed no abnormality in the child with the mildest clinical disease. Both of the other children showed abnormal hemidesmosomes on E.M. Abnormally weak immunoreactivity against Basal cell alpha 6 beta 4 integrin and the basement membrane glycoprotein nicein was noticed in the most severely affected child. Laryngo-onycho-cutaneous syndrome may, therefore, represent a new and distinctive type of junctional epidermolysis bullosa which is inherited in an autosomal recessive manner.

Table I. Proposed classification of aplasia cutis congenita (Frieden 1986) (2)

Category	Body area affected	Associated abnormalties	Inheritance
Group 1: Scalp ACC without multiple anomalies	Scalp, usually vertex	Cleft lip and palate: tracheoesophageal fistula; double cervix and uterus; patent ductus arteriosus; omphalocele; polycystic kidney; mental retardation; cutis marmorata telangiectatica congenita	Autosomal dominant or sporadic
Group 2: Scalp ACC with associated limb abnormalities	Midline scalp	Limb reduction abnormalities; 2-3 syndactyly; clubfoot; nail absence or dystrophy; skin tags on toes; persistent cutis marmorata; encephalocele; woolly hair; hemangioma; heart disease; cryptorchidism; postaxial polydactyly (1 family	Autosomal dominant
Group 3: Scalp ACC with associated epidermal and organoid nevi	Scalp, may be asymm-etric	Corneal opacities; scleral dermoids; eyelid colobomas; psychomotor retardation; seizures	Sporadic
Group 4: ACC overlying embryologic malformations	Abdomen, lumbar skin, scalp; any site	Meningomyeloceles; spinal dysraphia; cranial stenosis; congenital midline porencephaly; leptomeningeal angiomatosis; ectopia of ear; omphalocele; gastroschisis	Depends on underlying condition
Group 5: ACC with associated fetus papyraceus or placental infarcts	Multiple, symmetric areas, often stellate or linear, on scalp, chest flanks, axillae and extremities	Single umbilical artery developmental delay; spastic paralysis; nail dystrophy; clubbed hands and feet; amniotic bands	Sporadic
Group 6: ACC associated with epidermolysis bullosa (EB): Blistering, usually localized, without multiple congenital anomalies	Extremities	Blistering of skin and/or mucous membranes; absent or deformed nails; metatarsus varus; congenital absence of kidney (seen in cases of recessive, dystrophic EB; dominant, dystrophic EB; and EB simplex)	Depends on EB type: on EB type: may be autosomal dominant or recessive

Widespread skin fragility with congenital anomalies	Large areas on extrimities and torso	Pyloric or duodenal atresia; abnormal ears and nose; ureteral stenosis; renal abnormalities; arthrogryposis; amniotic bands; nail dystrophy	Autosomal recessive
Group 7: ACC localized to extremities without blistering	Pretibial areas; dorsal aspects of hands and feet; extensor areas of wrists	None	Autosomal dominant or recessive
Group 8: ACC caused by specific teratogens	Scalp (with methimazole); any area (with varicella and herpes simplex infections)	Imperforate anus (methimazole); signs of intrauterine infection with varicella and herpes simplex infections	Not inherited
Group 9: ACC associated with malformation syndromes	Scalp; any location	Trisomy 13; 4p - syndrome; many ectodermal dysplasias; Johanson-Blizzard syndrome; focal dermal hypoplasia; amniotic band disruption complex; XY gonadal dysgenesis	Varies, depending on specific syndrome

ACC= Aplasia Cutis Congenita
EB= Epidermolysis Bullosa

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