

## CUTANEOUS SQUAMOUS CELL CARCINOMA IN CHILDREN

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### ABSTRACT

The article objective consists in approaching a rare condition in children, the cutaneous squamous cell carcinoma (cSCC), whose frequency may become higher due to risk factors accumulation. Analyzing the few data furnished through available scientific literature, centered mainly on adult pathology, there have been outlined required data for the pediatric diagnosis and treatment of cSCC. Therefore, adopting a proper management for children particularities becomes a necessity.

**Keywords:** carcinoma, child

### INTRODUCTION

The skin is known to be the largest organ of the body, covering exceedingly 15% of body mass. Histologists and pathologists divide human skin into two compartments: epidermis and dermis, which have mesenchymal, epithelial, neurovascular and glandular components, varying in quantity and size, depending on the area of the human organism. The physical barrier between the human insidings and the outer environment is represented by the epidermis, a layer constituted especially by keratinocytes, working as a shield that protects against varying stressors like ultraviolet light, chemicals and radiation. These cells are connected with each other through tight junctions and desmosomes and have ectodermic origins. The epidermis is, typically divided into four layers: stratum basale, stratum spinosum, stratum granulosum and stratum corneum. The basal layer is known to be the germinative or stem layer, being constituted of cuboidal cells that have mitotic activity, these being connec-

ted, with each other, through hemidesmosomes, placed on top of a basement membrane. Through the activity of different promoting factors, from the basal layer of epidermis will appear the squamous cell carcinoma, both in adults and children. The dermis, frequently involved in tumor invasion and spreading, is also divided into two other regions – superficial and profound – with mesodermic embryological origins, contains adnexial structures of the skin, that is, sebaceous and sweat glands, hair follicles, nerves, immune cells, fibroblasts (1,2).

### INCIDENCE, RISK FACTORS AND CLASSIFICATION

Squamous cell carcinoma of the skin (cSCC) is a frequent pathological entity, being the main cause of death in adult patients with non-melanoma skin cancers, with an overall annual incidence of 700.000 cases that accounts almost 20% of all skin malignant tumors. From these patients, 4% of cases develop nodal metastasis and 1,5% die because of the

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cSCCs. The actual trend for incidence is in rising, as this evolved from 50% to 200% in the past 30 years. Therefore, with so many new cases to appear as time goes by, the possibility increases significantly for the existence of new cases with poor outcome and early metastatic spreading, upgrading the cSCC to an important health issue national and worldwide (3). As many scientists agree upon, in children, chronic immunosuppression is becoming an important factor risk for cSCCs, observed in many renal allograft recipients and stem cell transplantation. Pharmacological risk factors, like voriconazole administration and subsequent phototoxicity, have been cited to be strongly correlated with the onset of cSCC in young patients, with a median age from 4.9 to 9 years old (4). In late 80's, the UK National Registry of Childhood reported an account for all primary skin cancers of 1% for all childhood tumors, with an annual incidence of 1.4 million per year, with 1.2 million for children under 14 years old (5). Nonmelanoma skin cancers (NMSC) include basal cell carcinoma (BSC) and cSCC, most being non-fatal, with a majority of BSC. NMSC occurs mainly in intensely sun-exposed skin regions of children with a fair skin, being very rare in black people. It seems that sun exposure for long periods is the main pathogenetic factor for NMSC, especially for in cSCC, because of the skin ultraviolet photodamage of DNA (6). Some authors state that half of American children experience sunburns during summer, especially those with high risk characteristics including fair skin, sporadic sunscreen products usage, inadequate protective clothing and excessive outdoor activities in plain sunlight. Girls have higher risk because they are more likely to "get a tan" during summer than boys. Indoor tanning seems to become an increasing risk factors that is similar to the classic sunburns, while the application of sunscreen seems not to have any significant influence on the uprising incidence of both skin melanoma and non-melanoma cancers in children, probably due to incorrect usage (7). Nowadays, the overall prevalence of NMSC in children remains negligible, excepting those cases disorders of the DNA repair, like xeroderma pigmentosum, and basal cell nevus syndrome. It is still unknown, yet, whether childhood sun exposure may become a factor risk for developing NMSC, and cSCC in particular, later in adulthood (8).

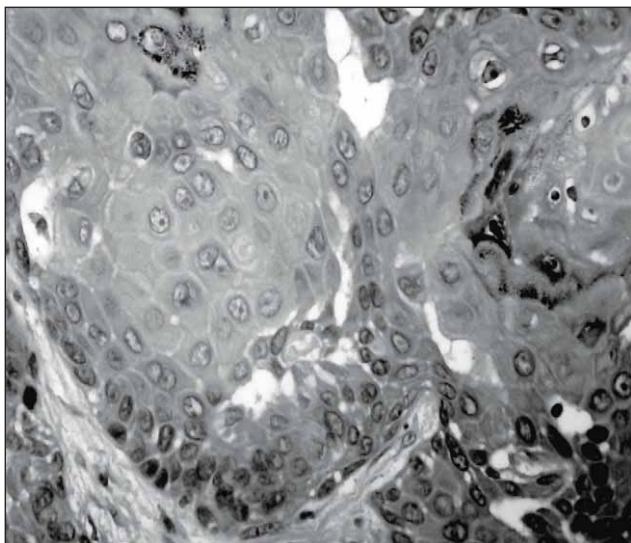
### GENETICS

The rare condition that expose children to the risk of developing cSCC is xeroderma pigmentosum (XP). Thus, XP is more frequent in Middle

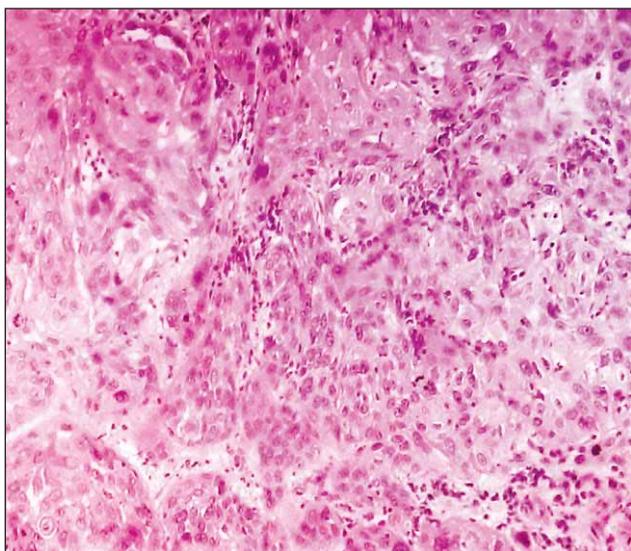
East and Japan, than in Europe. It is an autosomal recessive condition that has as its main feature the persistent erythema in the first year of life when the child become more frequently exposed to sunlight, thus to ultraviolet radiation. This disease implies many defective gene locuses regulating the DNA repair in the keratinocytes exposed to UV light, like XPA (9q22.3) that maintains single stranded DNA during repair, a 3'-5' DNA helicase known as ERCC3 (2q21) and, also, their family (ERCC2, ERCC4, ERCC5, ERCC1), and XPC (3p25) gene implied in DNA damage and global genome repair. Other hereditary conditions are the self-healing epithelioma of Ferguson Smith, epidermodysplasia verruciformis, dystrophic epidermolysis bullosa and porokeratosis (9).

### DIAGNOSIS: CLINICS AND PATHOLOGY

The tumor is described as a hard plaque or a papule, often with opalescent feature, with telangiectasias, developing central ulceration with crusts. Borders become elevated and indurated. High risk locations for metastasing are lips, perioral regions, ears, genitalia and periorbital areas. The diagnosis is mainly confirmed by skin biopsy, preferable trough excision, and subsequent histopathology examination (10). The pathological classification describes two entities, depending on the depth of invasion into the dermis, beneath the epidermis: cSCC in situ and invasive cSCC. The "in situ" variant is part of the Bowen's disease and erythroplasya of Quyerat – practically, not described in pediatric population, in modern literature. In general practice, it is used four histologic grades of differentiation for invasive cSCC from G1 (well differentiated) to G4 (undifferentiated), but this scale may differ from one center to another. Histologically, the invasive cSCC is composed of sheets of malignant cells, with squamoid features, with a degree of pleomorphism of nuclei and cell shape, with conspicuous nucleoli, atypical mitotic figures and necrosis (Fig. 1, Fig. 2). There might be different keratinization degrees, that are proportional with the differentiation degree of the tumor: the less keratin is produced, the more malignant and invasive the cSCC becomes. Therefore, by definition, the keratinised cSCC is well differentiated (G1) (11). Further tests may be performed, including immunohistochemistry that will show positivity for AE1/AE3 cytokeratins, CK5, p63 protein and epithelial membrane antigens (EMA), with absolute negative stains for S-100 protein (12). The main prognostic factor seems to be the dimension of the



**FIGURE 1.** Invasive Squamous cell carcinoma – microscopic aspect, H&E, 10 x 10, showing tumour, pleomorphic cells, grouped in sheets, penetrating the dermis (personal collection).



**FIGURE 2.** Invasive squamous cell carcinoma – microscopic aspect, H&E, 4 x 10, showing sheets of malignant cells invading the dermis, necrosis, few atypical mitotic figures, keratin formation and scant inflammatory infiltrate (personal collection)

entire lesion: if this is lower than 2 cm, than the stage is I, else (> 2 cm) the stage is II. Stage III patients have clinical, histological or radiological evidence of one node metastasis measuring over 3 cm and direct extension into bone – mandible, orbit, maxilla, temporal bone – while stage IV patients have tumors with perineural invasion of skull base or axial skeleton, two or more lymph node metastasis or a single node measuring more than 3 cm in size. Also, stage IV is agreed upon, when it is detectable distant site metastasis. The pediatric on-

cologist will require tumor thickness, Clark's level, the presence of perineural invasion, primary site on hairy region of lips or ear, the histologic grade, and size of the largest lymph node (13). Differential diagnosis should include ulcerative lesions, like syphilis chancre and keratin producing lesions, actinic keratosis and keratoachantoma.

## TREATMENT

The treatment is very similar with that used in adults. It is generally applied the Mohs surgery technique – resection with frozen section biopsy – and with this method perineural invasion seems better to evaluate, in order to assess resection margins more accurately (14). Other techniques used are cryotherapy, classic surgery, topical treatment and photodynamics. Radiation therapy is generally used in adults with large, invasive and less operable tumors, and should be indicated cautiously in children. Systemic chemotherapy is used for patients that developed metastatic disease. Oral capecitabine or, its active form, oral 5-fluorouracil, with subcutaneous interferon alfa for 2 to 3 weeks, have been studied in locally advanced cSCC disease in adults, with promising results. Cetuximab and gefitinib, known as EGFR inhibitors, associated with 5-fluorouracil and cisplatin, have increased the patient survival rate (15).

## CONCLUSION

The cSCC in children is, yet, a very rare medical, pediatric, condition. There are few scientific data regarding this pathology and its management in children. Through a rising incidence, due to sunlight exposure and nowadays cosmetic habits for the young patients, any ulcerative lesion on skin, evolving, especially, in those areas that are exposed to ultraviolet radiation should be carefully observed and treated, as survival rate in case of cSCC diagnosis is far better in pediatric population, especially in early detection.

## ACKNOWLEDGEMENTS

We wish to send our special thanks to the University of Medicine and Pharmacy “Carol Davila” in Bucharest, the Faculty of Medicine, the funded Doctoral school, to the Central Library of this university and its staff.

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