CUTANEOUS METASTASES IN CHILDREN. A HISTOPATHOLOGICAL CASE REPORT AND REVIEW.

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Abstract: *Cutaneous metastases are a rare finding in children, being diagnosed usually after primary tumour discovery, however it may be the first sign of a malignancy. Therefore, the origin tumour could be diagnosed through the pathological findings, but in most cases this is impossible due to scant amount of tissue involved in the metastasis. This article tries to approach, through available scientific literature and procedures, an unidentified carcinomatous metastasis discovered in a 14-year old boy, proving to be an undifferentiated epithelial tumour. The importance of cytokeratines CK7 and CK20 is discussed, together with histological distinctive characteristics of other tumours that may metastasize and differential diagnosis with primary adnexal carcinomas that may mimic skin metastases.*

INTRODUCTION

Metastasis is defined as a neoplastic lesion arising from another neoplasm that has no further continuity with it. Skin metastasis is defined as a spread of malignant cells from a primary malignant tumour to different regions of the skin. Cutaneous metastases (CM) have an increasing incidence in children nowadays, when histological detection is more accurate to lower ages, especially when differential diagnosis for benign conditions is taken in account. Skin secondary tumours appear as a consequence of primary tumour development, mostly soft tissue, being dependent on vascular or lymphatic spreading.(1) Many cases have been reported regarding all types of malignancies metastatic to skin, but few systematic attempts have been made to consider a pattern of apparition. No matter what the size and condition of the specimen might be, most carcinomatous metastases might be classified as adenocarcinoma, squamous cell or undifferentiated. Skin secondary malignancies with visceral origin are very important for dermatologists, pathologists and surgeons because of their multiform clinical presentation, while diagnosis delay might become dangerous for the child outcome.(2) Furthermore, CM might be the very first sign of a developing cancer or a recurrent tumour condition. The suspicion is raised by the pediatric doctor, while the surgeon and the pathologist might elaborate a final diagnosis. Therefore, rapid intervention becomes mandatory, while the survivability of a patient with a cutaneous metastasis is low being around 7.5 months.(3) The most frequent site of the CM are the abdomen skin (26%), followed by head and neck (25%), arms, legs, trunk, axillae, shoulder and anus. In females, 75% of cases are located on the anterior aspect of the abdomen and chest, while in men, the election region remains the anterior aspects of head and neck region. The back skin is a rare site for metastasis. The pathologists describe four main characteristics in CM: nodular, infiltrative, diffuse and intravascular.(4)

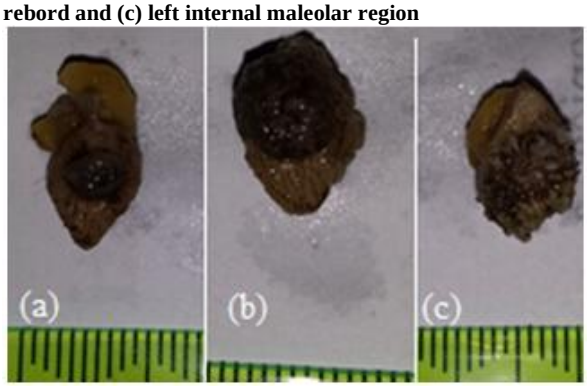
PURPOSE

The purpose of this article is to report a case of a difficult to diagnose cutaneous metastases in a child together with a comprehensive review of literature for the matter, as this subject is almost disregarded by pathologists, in particular, and medical researchers, in general.

MATERIALS AND METHODS

A 14-year-old boy presented to the Dermatologist office in our hospital for 3 melanocytic-like lesions: (a) first on posterior aspect of the right thorax, (b) the second at the right costal rebord and (c) the last located on the left internal maleolar region (figure no. 1). The macroscopic appearance of the first lesion was that of an elevated, ovoid, brownish circumscribed lesion – 0.4/0.3/0.2 cm – while the second lesion (b) had larger dimensions – i.e, 0.7/0.7/0.3 cm – being almost spherical, bulging at the site. The third one (c) was also ovoid, but more irregular coloured – brown and white alternant areas – with an gritty aspect, and intermediate dimensions, approximately 1.0/0.6/0.4 cm. The routine clinical and biological examination of the child revealed no abnormalities, having no paraclinical deviations (figure no. 1).

Figure no. 1. Macroscopic aspect of resected specimens for supposed naevi (buffered formalin 10%): (a) the lesion in matter - posterior aspect of the right thorax; (b) right costal rebord and (c) left internal maleolar region



The young patient was referred to the Surgical Department where resections have been made for the above mentioned lesions, within safety margins, and the obtained

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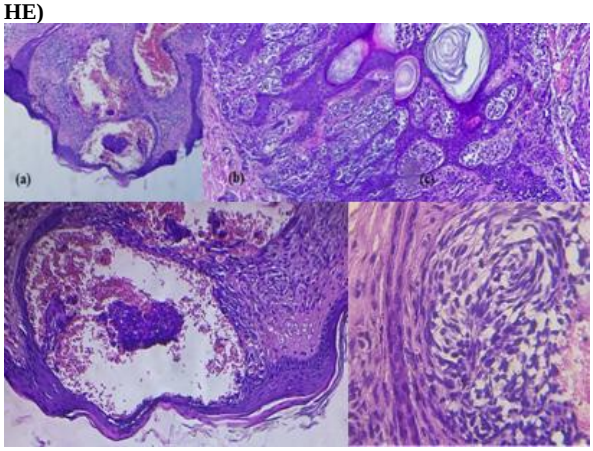
rhomboidal-shaped specimens were referred to the Pathology Department. The tissue samples were fixed in buffered formalin 10%, and processed in our laboratory in successive alcohol grades (70°, 80°, 96°), paraffin embedded, sectioned and stained through standard procedure for haematoxilin and eosin.

RESULTS

At microscopic examination, the second lesion showed a keratoachantoma-like appearance, junctional melanocytic activity, with type B and C melanocytes and rare melanosomes, arranged in compact groups, located between the rete ridges, with no mitotic activity or atypia. However, the third lesion proved more cytological activity, with slight melanocytic atypia and normal mitoses (0-3/10 HPF), bridging of adjacent, irregular, rete ridges, lentiginous proliferation of hyperchromatic, epithelioid and spindled melanocytes at dermoepidermal junction. Therefore, the final diagnosis for the second (b) and third (c) resected masses remains that of a (b) compound melanocytic naevus, respectively, (c) Clark or dysplastic naevus (figure no. 2).

Figure no. 2. Histologic aspects of resected specimens: (a) cutaneous metastases of unknown epithelial origin, ectatic vessels and spindle, clear, cell dermal perivascular, infiltrative pattern (4x10, HE); (b) histological aspect of a compound naevus with dermoepidermal junctional melanocytic activity, arranged in compact groups (10x10, HE); (c) dysplastic melanocytic groups situated at the tip of connected rete ridges and architectural pleomorphism (10x10, HE); down - details from lesion (a): left – intravascular cell group, with clear cell-like dystrophy, floating inside the lumen, surrounded by infiltrative pattern; right – infiltration of whorled, plexiform, spindle cell with clear cytoplasm, that delineates angiomatoid spaces (10x40, HE)



The first lesion (a) presented as a nodule, with ectatic vascular, angiomatoid, spaces developed within an capillary haemangioma, confined to the dermis, with epidermal hyperkeratosis and rete ridges effacement. These vessels showed no endothelial lining, being delineated by a plexiform, clear cell population, with a central, pyknotic and hypercomatic nuclei, with no atypia or mitoses, having an infiltrative, spindle shaped pattern and an epidermolitic activity. Within the vascular lumina, free floating glomeruloid, whorled, cellular groups were detected, having slight atypia and some intracytoplasmic vacuoles, probably containing lipids that were consistent with an unspecifiable epithelial origin (figure no. 2). The final diagnosis was that of an undifferentiated invasive carcinoma metastasis as the infiltrative behaviour corresponds with this kind of tumour, i.e, spindle, plump rounded cells, focally with clear cell features suggesting a high grade pleomorphical neoplasm. Renal cell carcinoma, angiosarcoma and Kaposi sarcoma were ruled out, as no morphological and paraclinical criteria sustained these entities for the case in matter. Also, atypical angiomatoid hyperplasia was in discussion, however vascular spaces are not so ectatic and the presence of intraluminal metastasis ruled out benign conditions. The child was referred to our local Oncological department for further investigation and treatment. Immunohistochemical analysis for the metastatic cells is out of discussion, as the necessary tissue volume is far insufficient for analysis.

DISCUSSIONS

Clinically, most skin metastases appear as a rapid-growing solitary or multiple mass, firm, flesh-coloured, round or oval, elevated lesion located in dermis or subcutaneous that may have a stationary evolution. Sometimes, palpation might prove a local painful indurated tumour.(5) The variability of presentations might include nodules, papules, plaques and ulcers. Other frequent clinical expressions are alopecia, morphea-like lesions, dermatofibroma-like or pyogenic granuloma-like lesions, herpetic-like eruptions or even cellulitis.(6) Histologically, CM are more chaotic than primary tumours, as CM involve collagen dissection and a rich vasculature with no epidermotrophic pattern. In children, renal cancer might be very frequent. Differential diagnosis with local evolving Kaposi sarcoma, pygenic granuloma or other vascular proliferations should be made with a CM of a renal cell carcinoma. In these situations, CM might simulate an abscess on the head, neck or face. Histologically, proximal renal tubular cells might become visible showing a trabecular, papillary or tubulopapillary pattern, with a proeminent vascular pattern, extravasation of red cells and hemosiderin, while the cells contain abundant glycogen and lipids, sometimes showing plexiform appearance.(7) Also, gastrointestinal tumours might express a nodule located in middle or lower dermis, forming glands, clusters or strands of neoplastic cells together with an intense desmoplastic reaction. Colorectal carcinomas, however rare in children, should not be disregarded as a possible condition. The CM of this particular cancer appear on skin as a "Sister Mary Joseph's nodule", with forming glands and intense mucin production. In the above described situations, Alcian-blue, periodic acid-Schiff, CDX2, CK7 and CK20, together with carcinoembryonar antigen and EMA should clarify the diagnosis.(5) Gynaecological malignancies rarely metastasize to skin, especially in children. However, cases have been cited of CM from ovarian tumours. Metastasis occurs mostly in scars at the sites of paracentesis, and present psammoma bodies, followed by a mucinous and endometrioid characteristic pattern. Breast carcinoma, although improbable in small children, becomes a serious condition in adolescents and young adults. In these situations, most CM has an undifferentiated pattern, while a well-formed duct pattern is less likely to be encountered. For instance, the pathologist may have difficulties in detecting breast lobular carcinoma CM. Although, CK7 and CK20 might help differentiating from a possible emergent digestive source, GCDFP-15 is a marker of apocrine differentiation in breast epithelium and might be used to confirm the mammary origin. In some cases, the breast malignant CM is further difficult to differentiate from a malignant melanoma, especially in epidermotropic metastases, as in-tumour melanocyte proliferation may occur. In heavy smoking adolescents, lung carcinoma may develop CM, located usually on the chest wall and posterior trunk, giving a clue for their origin. It is well known that lung small cell carcinoma is characteristically involving back skin. Differentials are made with primary Merkel

cell carcinoma (CK20 positive and thyroid transcription factor 1 – TTF1 negative), squamous cell carcinoma and metastastic digestive carcinomas, while lung small cell cancer is CK20 negative and TTF1 positive.(8) Sarcomas might deliver CM as an inaugural disease manifestation, like in a femural osteosarcoma case, presented as two scalp nodular tumour.(9) Rare soft tissue tumours, like alveolar soft part sarcoma CM to scalp areas in a 21-year-old man, were cited, but molecular analysis was required to identify the primary tumour, with RNA extraction and reverse transcriptase polymerase chain reaction in order to detect a specific genetic locus, called transcription factor 3, as this kind of neoplasm may have a close resemblance with renal cell cancer on standard stains.(10) Therefore, routine differentials for sarcomas or soft tissue neoplasms are almost impossible, requiring molecular biology techniques. In order to sustain a diagnosis, the pathologist may need to differentiate between primary cutaneous tumours and secondary metastases. Thus, primary adnexal carcinoma may mimic the pleomorphic multitude of cutaneous metastases, however these are very rare in children. Ductal eccrine carcinoma may mimic a ductal breast neoplasm metastatic to skin, while mucinous variant may, very well, resemble a gastrointestinal CM. However, some authors sustain that these lesions are easy recognisable on routine stained sections. Although rare, high grade spindle cell sweat gland carcinoma, having a whorled, organoid, concentric pattern might be similar to nasopharyngeal CM.(11)

CONCLUSIONS

Although any form of malignant tumour may metastasize to skin, in current practice there is a small number of neoplasms that are likely to do so. Immunohistochemical profiling is mandatory, especially regarding CK7 and CK20, however, in undifferentiated carcinomas CM the antigen panel is almost impossible to apply as, in most cases, some like ours, there is no sufficient tumoral tissue for all molecular analysis possibilities. Therefore, interdepartmental approach – surgeon, pathologist, oncologist and radiologist – for this kind of situations must be accomplished for most accurate diagnosis.

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