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CLINICAL REPORT

Cutaneous Location of Atypical Teratoid/Rhabdoid Tumour

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Atypical teratoid/rhabdoid tumour is a rare and highly malignant tumour of the posterior fossae nervous system that occurs in children especially in the first few years of life. Cutaneous location is not previously reported. A newborn boy was referred for both aqueductal stenosis detected antenatally and skin tags mimicking hamartoma. The cerebral tumour increased in size during a few months leading to both skin and cerebral biopsies. Integrase Interactor-1 (INI-1) immunostaining and tumoural and leukocytes *INI-1* gene sequencing confirmed the atypical teratoid/rhabdoid tumour nature of the cerebral tumour. INI-1 immunostaining in skin biopsy confirmed the dermal location of rhabdoid tumour. Thus, unusual cutaneous lesions may be part of atypical teratoid/rhabdoid tumour. The loss of Integrase INI-1 on immunohistochemical staining is characteristic. ***Key words: Atypical teratoid/rhabdoid tumour; skin metastasis; prenatal diagnosis; Integrase Interactor-1.***

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Atypical teratoid/rhabdoid tumour (AT/RT) is a rare and highly malignant tumour of the central nervous system (CNS), first described in 1987 (1). This tumour is usually diagnosed in children under 2 years. The true incidence of AT/RT is unknown, but they stand for 1 or 2% of paediatric brain tumours and European data suggest 0.1–0.5 per million children per year (2). AT/RT can occur anywhere in the CNS. The common locations are the cerebellopontine angle and cerebellar hemispheres. Supratentorial location is less common, including suprasellar, pineal and temporal lobe (2–6). Histologically, AT/RTs are typically composed of rhabdoid cells, often with primitive neuroectodermal cells characterised by divergent differentiation among epithelial, mesenchymal, neuronal and glial lines. AT/RT often present with metastatic disease, particularly leptomeningeal dissemination and the overall prognosis is poor. The extra-CNS sites of AT/RT's metastasis are liver and lung (2–6). Treatment of AT/RT requires multimodal therapy involving surgery, chemotherapy, and radiotherapy. The predictive factors of poor outcome are young age (in part due to restrictive use of radiotherapy), metastatic disease, infratentorial location, and less than complete remission at the end of chemotherapy (6). The loss of Integrase Interactor-1 (INI-1) expression on the immunohistochemistry is characteristic. It is a consequence of bi-allelic inactivation of the tumour suppressor gene *INI-1* (also known as *SMARCB1*; *hSNF5*, or *BAF47*) located at chromosome 22q11.2. INI-1 is a subunit of SWItch/Sucrose Non Fermentable complex (SWI/SNF) of proteins, known to regulate ATP-dependant chromatin remodelling exposing DNA for transcription and tumour activating pathways (7, 8). We report, to our knowledge, the first case of cutaneous metastasis of AT/RT.

CASE REPORT

A newborn was referred to dermatology for 3 congenital lesions of the buttock and right temple (Fig. 1). He was born at gestation week 38 (GW) from unrelated parents. Antenatal history was remarkable. The 24th GW ultrasound showed ventriculomegaly. Repeated ultrasound at 32 GW showed hydrocephalus; therefore the diagnosis of aqueductal stenosis was evocated. Two cerebral magnetic resonance imaging (MRI), performed at week 34 GW and 36 GW confirmed the hydrocephalus by aqueductal stenosis (Fig. S1a[1]). The pregnancy went on and the delivery was triggered at 38 GW, considering the importance of hydrocephaly, by caesarian.

At birth, neurological examination was normal. At day 2, cerebral MRI showed a 7 mm parenchymal lesion of the mesencephalic tectum, responsible of the antenatal hydrocephalus by aqueductal stenosis (Fig. S1b[1]). Endoscopic third ventriculostomy was performed, allowing ventriculomegaly reduction.

Skin examination showed 3 lightly erythematous papules, two on the right temple, and the third one on the left buttock. The lesions seemed to be verrucous, as observed with verrucous hamartomas. Histopathological analysis of the buttock lesion showed an exophytic lesion, surmounted by a discreetly hyperplastic epidermis, involving every layer. There was no cytological modification. There was an important superficial dermis oedema, with many capillaries, and round unpigmented and atypical cells, filling the dermal papillae. The reticular dermis was completely normal. The immunohistochemistry with anti-human papillomavirus (HPV) antibody was negative. There were many CD3 lymphocytes and a few macrophages.

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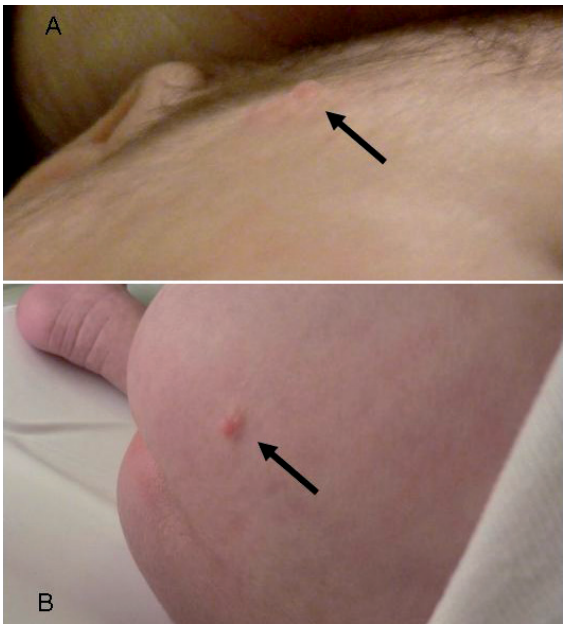

Fig. 1. Skin features at birth. Papules of the right temple (*arrow*, a), and the left buttock (*arrow*, b). The lesions were surmounted by epidermic papillomatosis.

The round cells were negative for CD31, CD1a, smooth muscle actin, S 100 Protein, CD3, myogenin, XIIIa factor and CD68. Ki67 evaluation showed a proliferation index of 15%. These puzzling round cells remained unidentified (Fig. 2) and the anatomoclinic confrontation did not permit an accurate diagnosis.

Two months after birth, the tectal lesion, had increased to 24 mm on cerebral MRI and a subependymal lesion, measuring 6 mm were detected. None of these lesions showed enhancement after gadolinium injection. A hypothesis of multiple hamartomas was proposed involving the cerebral tissue and the skin. Germ-cell markers titration on cerebrospinal fluid, after rachicentesis, was negative.

The cerebral lesions grew at 4 months (Fig. S1c, d[1]). Therefore, a cerebral endoscopic biopsy was performed. Histology showed a monomorphic tumoural proliferation characterised by small undifferentiated cells with irregular contours. There were no typical rhabdoid cells with standard stains. On immunohistochemistry, tumour cells expressed glial (glial fibrillary acidic protein, oligodendrocyte transcription factor 2), neuronal nuclear antigen, epithelial membrane antigen (EMA) and mesenchymal markers (smooth muscle actin). Tumour cells were negative for cytokeratin AE1/AE3, cytokeratin-18, and Octamer-binding transcription factor-3/4. The proliferation index reached 60% and no p53 (Protein 53) nuclear accumulation was seen. The histopathological diagnosis was AT/RT, based on complete loss of INI-1 expression in tumour cells.

Retrospectively, the INI-1 staining of the cutaneous biopsy of the buttock lesion showed a complete loss of expression on the atypical cells (Fig. 2c). Therefore, the cutaneous lesion was considered as a cutaneous location of AT/RT.

The right temple skin lesion was removed while cerebral biopsy was performed. Histopathology showed an exophytic lesion covered by a mild acanthotic epidermis. The underlying connective dermis was composed of well-vascularised, loosely arranged collagen. There was a mild mononuclear cell inflammatory infiltrate made up of CD3 lymphocytes. There were no atypical cells and INI-1 marked all the inflammatory cells. This pattern was similar to those usually seen in skin tags. However considering the age of the patient and that the lesion was present at birth this lesion is likely to be a connective naevus (hamartoma). The abdominal ultrasound and the chest X-ray were normal.

HSNF5/INI-1 gene sequencing showed a homozygote deletion (c.351delC in exon 3) leading to a truncated protein (p.Thr118ProfsX25). In leukocytes DNA, the same mutation was detected heterozygously.

The patient was treated with multiagent chemotherapy, including vincristine, methotrexate, doxorubicin, cyclophosphamide, etoposide and cisplatin. Polychemotherapy did not prevent tumour progression and CNS metastatic dissemination. At 8 months, he was still on palliative care at home. Skin examination remains unchanged.

DISCUSSION

Malignant RTs are encountered in kidney, soft tissues and CNS, the latter being called AT/RTs. The term RT reflects the common occurrence of rhabdoid morphology (large, polygonal, eccentrically place, vesicular nuclei, prominent nucleoli and intracytoplasmic eosinophilic inclusion). CNS and peripheral RTs have been associated with biallelic inactivation of the *hSNF5/INI-1* tumour suppressor gene. Patients with germline mutations of *INI-1* are predisposed to RTs of brain, kidney, and soft tissues, and may present within the first year of life with multiple metachronous tumours. Isaacs (9), in a 40-year systematic review of the literature of foetal and neonatal RTs, estimated that concomitant brain tumour is found in almost 1/3 of foetuses and neonates with renal or extrarenal RTs. The CNS involvement occurred more often in patients with renal RT than in those with extrarenal RT. Metastatic disease at diagnosis was noted in 1/3 of the patients with CNS RT. The usual AT/RT metastases are localised in lungs, liver and other locations in CNS (mainly cerebrospinal pathway). Cutaneous metastases by non-haematopoietic childhood malignancies are rare, and are mainly due to rhabdomyosarcoma and neuroblastoma (10, 11). Cutaneous metastases of malignant rhabdoid tumour have only rarely been reported, and the primary tumours were soft tissue and renal RT (12–14). Cutaneous RT can also rarely mimick haemangioma (15).

In paediatric studies, there is no case of cutaneous metastases from brain tumours. Our patient presented with two different locations at birth, cerebral and cutaneous, which has never been described before. The nature of the cutaneous location in our case is surprising. Two of the 3 clinically similar lesions were analysed, and there was only one with cutaneous location of AT/RT. A primary rhabdoid skin tumour has been reported in a 14-month-old child. Clinically, it presented as a multipolypoid gross lesion (14).

These findings suggest two hypotheses. Firstly, germline mutations of *INI-1* in our case predisposed the foetus to AT/RT and cutaneous malignant RT, by loss of heterozygosity of *INI-1*. Secondly, the cutaneous location corresponded to CNS AT/RT metastasis. Interestingly in this case, AT/RT cutaneous location mimics cutaneous hamartomas.

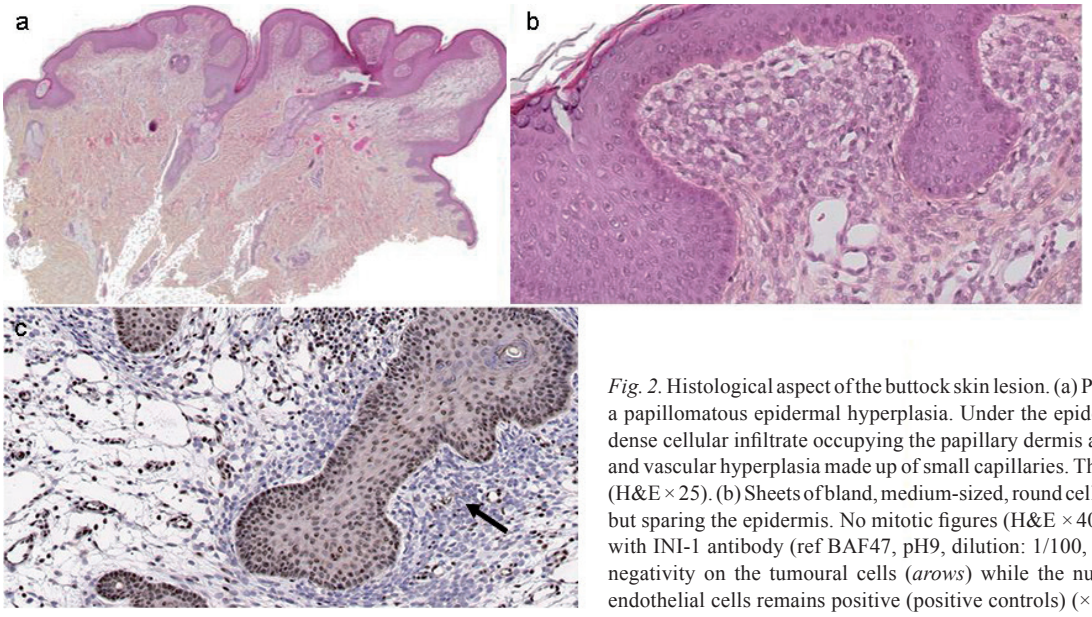

Fig. 2. Histological aspect of the buttock skin lesion. (a) Pedunculated lesion showing a papillomatous epidermal hyperplasia. Under the epidermis there is a moderately dense cellular infiltrate occupying the papillary dermis and associated with oedema and vascular hyperplasia made up of small capillaries. The reticular dermis is normal (H&E × 25). (b) Sheets of bland, medium-sized, round cells filling the papillary dermis but sparing the epidermis. No mitotic figures (H&E × 400) and (c) Immunostaining with INI-1 antibody (ref BAF47, pH9, dilution: 1/100, BD sciences) shows a total negativity on the tumoural cells (*arows*) while the nucleus of keratinocytes and endothelial cells remains positive (positive controls) (× 250).

The histogenesis is still unclear. The tumour cells show immunohistologic diversity with a unique combination of rhabdoid cells, neurologic, peripheral epithelial and mesenchymal elements, but the tumour lacks the divergent tissue development pathognomonic of malignant teratomas. The rhabdoid cells express vimentin, EMA, and smooth muscle actin and may have mindbomb E3 ubiquitin protein ligase 1 (MIB-1) labelling indices of 50% to 100% indicating rapid growth. Markers of germ cell tumours are not expressed: placental alkaline phosphatase, Oct4, c-KIT, CD30, α-foetoprotein, and β-human chorionic gonadotrophin (7). It is of note that Sall4 can be expressed in 88% of cases (16). Many proposals highlight the histiocytic, mesenchymal, meningeal, neuroectodermal, or even germ cell lineage of AT/RT.

Regarding the antenatal diagnosis of AT/RT, it has already been described, with the following main presenting signs: macrocephaly, hydrocephalus, and intracranial mass (9). Hydrocephalus detected by antenatal ultrasound can be related to a brain tumour and may alert clinicians. Unusual cutaneous lesions may be part of AT/RT. The loss of Integrase INI-1 on immunohistochemical staining is characteristic.

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