Desmoplastic Neuroepithelial Tumor of Infancy in the Nevus Sebaceus Syndrome:
Report of a Unique Constellation and Review of the Literature

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Summary

The nevus sebaceus syndrome (NSS) is a neurocutaneous disorder characterized by unilateral hyperplasia of skin appendages and skeletal hemihypertrophy, hemimegalencephaly, or hemiatrophy along with disabling seizures. Despite the proneness of the dermal stigmata to eventually undergo neoplastic transformation, the malformative lesions of the central nervous system rarely evolve into frank tumors. We present the case of a 10-year-old girl with left-sided sebaceous nevi, ipsilateral enlargement of the skull, and a desmoplastic neuroepithelial tumor (DNET) in the right fronto-parietal area of the brain. The tumor was removed by surgery. Histologically, it corresponded to a mitotically active small-cell anaplastic astrocytoma with genuine desmoplasia. Investigative methods included immunohistochemical positivity for glial fibrillary acidic protein, lack of expression of neuronal markers, and ultra-structural documentation of sheaths of basal lamina and collagen around tumor cells. A survey of the literature of brain tumors associated with NSS revealed two cases of histologically verified pilocytic astrocytomas, and one each of a choroid plexus papilloma, a mixed glioma, and a meningioma, as well as a subependymal giant cell astrocytoma – the latter possibly in an overlap syndrome of NSS and tuberous sclerosis. We hypothesize that the tumor described herein, one involving both atypical differentiation and enhanced growth potential, is paradigmatic of neuropathological events to be expected in the NSS.

Key words: Nevus sebaceus – Desmoplastic neuroepithelial tumor of infancy – Multiple tumors

Introduction

Neurocutaneous syndromes are perceived clinically as a constellation of constitutional anomalies involving parts of the integument and bones, and associated with various neuropsychiatric disabilities [16, 24]. In addition, many patients suffering from some kind of phakomatosis are also at increased risk of developing malignancies. From the biological point of view, phakomasotes are conceived as a defect of cells to properly self-organize into organoid structures, i.e., one of programmed migration, differentiation, and proliferative potential.

The NSS is characterized by unilateral hyperplasia of skin appendages, hemihypertrophy of bones and soft tissues with hemimegalencephaly or hemiatrophy of the brain, and mental deterioration due to intractable seizures [5, 16, 24]. The neuropathology of NSS has been incompletely explored. Specifically, there is an ostensibly poor relationship between hamartomatous changes customarily regarded as preneoplastic lesions and frank central nervous system tumors.

In the following, we present the case of a 10-year-old girl with NSS who developed a supratentorial desmoplastic cerebral astrocytoma of infancy (DCAI) tentatively diagnosed as anaplastic. Similar tumors have also been referred to as DNET.

To the best of our knowledge, this is the first report of such an occurrence. We speculate that the association...
might not have been purely fortuitous; it might rather fit into the paradigm of misplaced pluripotential stem cells with loss of growth control.

Case History

The patient, a 10-year-old girl at the time of her present admission, has been presenting the cutaneous stigmata of NSS on the left face and neck since her birth. In addition, discrete ipsilateral hemihypertrophy of the skull was evident (Fig. 1 – left). Her past medical history is noticeable for the removal of a frontal skin nodule diagnosed as “lipofibroma” at five years of age. At ten, she started developing left-sided Jacksonian epileptic fits with secondary generalization. Seizure control was unsuccessful despite combined antiepileptic medication. Interictal electroencephalograms revealed only irregular waves over the right frontal region.

Cranial MRI scans disclosed a superficial contrast-enhancing tumor, 2.5 cm in diameter, localized in the adjacent cortices of the superior and middle frontal gyri of the right precentral area (Fig. 1 – right). The lesion was approached via a right frontal craniotomy and completely removed. The surgeon’s impression was that of a sharply demarcated line of cleavage along the brain/tumor interface, and the lesion was not attached to the dura mater. Postoperatively, the child underwent 30 cycles of 1.8 Gy radiotherapy to the tumor bed. Six months after surgery, the patient is on anti-epileptic medication and is doing reasonably well.

Materials and Methods

Biopsy specimens were fixed in 6 percent buffered formalin and routinely processed in paraffin. Histochemical stains included hematoxylin-eosin (H&E), periodic-acid-Schiff (PAS), and Sweet-Gordon’s reticulin impregnation method. Immunohistochemistry was performed on 2 µm tissue sections. Primary antibodies included glial fibrillary acidic protein (GFAP, polyclonal 1:300), vimentin (monoclonal 1:1000), S100 protein (monoclonal 1:500), epithelial membrane antigen (EMA, monoclonal 1:10), neurofilament protein triplet (monoclonal 1:100), synaptophysin (monoclonal 1:100; all previous sera manufactured by DAKO®, Glostrup, Denmark), and MIB-1 (monoclonal 1:10, Dia 505® Milan, Italy). Immunoreactivity

Fig. 1. Left: Patient’s face dysplaying slight left-sided hemihypertrophy and near-linear papular skin eruptions along the nasolabial fold. Right: Gadolinium-enhanced coronal T1-weighted MRI scan of the brain reveals bright contrast medium uptake by tumor. On the right frontoparietal convexity. Note discreet convolutional anomaly of adjacent gyri, as well as evidence of ipsilateral brain atrophy.
was detected using a standard two-step procedure involving swine-anti-rabbit or rabbit-anti-mouse immunoglobulins, and a non-avidin-biotin based detection system (EnVision® DAKO, Glostrup, Denmark). Immunolabeling was visualized with aminoethylcarbazol as chromogen. For ultrastructural study, selected areas were excised from one of the paraffin blocks and routinely reprocessed (Taab® 812 medium) for ultrathin sectioning. One to three uranyl-acetate and lead-citrate contrasted grids were viewed in a Philips CM 10 transmission electron microscope.

**Histological Findings**

Light microscopy revealed an overtly hypercellular, compact-textured neoplasm composed in part of mesenchymal-like sheaves of elongated cells. Most of the latter were invested by an elaborate network of PAS-positive and argentaffin reticulin fibers ensheathing individual cells. Focally, tumor cells tended to have carrot-like nuclei and scarce cytoplasm resembling undifferentiated medullary epithelium (“small round blue cells”) reminiscent of a primitive neuroectodermal tumor (Fig. 2). Mitotic figures were irregularly distributed, with some high power fields (×40) containing several dividing nuclei. The brain/tumor interface was blurred by infiltrating tumor cells.

Immunohistochemistry for GFAP highlighted stout bipolar processes or juxtangular caps in most tumor cells, thereby confirming their astrocytic nature. A similar reactivity was noted for vimentin and S-100 protein. The proliferation marker MIB-1 decorated up to 7 percent of neoplastic nuclei. Neuronal markers including synaptophysin and neurofilament proteins were nonreactive. The same was true for the epithelial membrane antigen, an epitope expressed by meningiomas. The biopsy lacked both glomeruloid neovascularisation and tissue necrosis.

Electron microscopically, despite poor organelle preservation, we were able to document neoplastic astrocytes rife with 6–9 nm intermediate filaments and

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**Fig. 2.** Microscopic appearance and immunophenotype of desmoplastic neuroepithelial tumor. **A:** Hypercellular texture composed of an admixture of anaplastic astrocytes and small undifferentiated cells; H&E – original magnification: ×400. **B:** Argentaffin basal lamina invest individual tumor cells and evoke a mesenchymal-like storiform pattern; Sweet-Gordon’s reticulin – original magnification: ×200. **C:** The majority of tumor cells show immunoreactivity to glial fibrillary acidic protein; GFAP – original magnification: ×200. **D:** MIB-1 labeling indices are unevenly distributed and may attain 7%; MIB-1 – original magnification: ×200.
covered by often discontinuous basal lamina abutting on bundles of collagen (Fig. 3).

On account of its light microscopic appearance, immunophenotype, and electron microscopic evidence of basal lamina, the structural details above were interpreted as being most consistent with DNET with astrocytic differentiation (DCA). Although DCAI is not accommodated in, i.e., defined by the revised version of the World Health Organization typing of central nervous system tumors, we felt that, by virtue of its vigorous mitotic activity, the present tumor qualified as anaplastic (grade III).

**Discussion**

Malignant supratentorial gliomas are distinctly rare in infancy and childhood. Conversely, a large scale of low-grade glial or glioneuronal neoplasms tend to specifically arise in this age group; several of them in the setting of dysontogenetic conditions customarily designated as phakomatoses [2]. The NSS has been established as part of this complex of diseases with the eponymous skin lesion and a wide variety of skeletal, ocular and visceral anomalies [5, 16, 24]. Although seizures along with mental retardation are its leading causes of morbidity, the neuropathological findings are poor and non-specific in most cases.

In two out of their three cases, Holden and Dekaban noticed only hemimegalencephaly and cortical atrophy, respectively [6]. The patient presented by Kang et al. had an arteriovenous malformation in the territory of the middle cerebral artery [8]. For want of histological documentation, the left temporal biopsy specimen reported on by Moskowitz and Honig as “meningoencephaloangioneuromatosis” might actually have been thought of as meningoangiomatosis, a non-neoplastic overgrowth of the leptomeninges [13].

We are aware of only six previous instances of frank central nervous system neoplasms in the maldevelopmental constellation of the NSS confirmed by histopathology [1, 4, 7, 9, 10, 18].

Levin et al. surveyed computed tomographic findings in 11 children with the disease. Only one choroid plexus papilloma (location not specified) was ascertained by surgery and subsequent pathological examination, whilst the presence of a lipoma of the corpus callosum and a germinoma of the pineal area were inferred from their radiological appearances [9]. Some forms of deformity of either cortex or subcortical structures were present in 10, and circumstantial evidence pointed to migrational abnormalities in four. Regarding the latter, Bosman et al. claim to differentiate cortical tubers and neuronal heterotopias of hemimegalencephaly on the grounds of their microscopic texture and immunophenotype [3]. The report by Hwang et al. of brain anomalies (cortical tubers and a subependymal giant cell astrocytoma) coexisting with dermal stigmata of NSS nevertheless suggests that the two entities may either overlap or constitute yet another form of phakomatosis [3, 7]. Levin’s paper is also a remarkable resource on the topic with references culled from the non-English literature.

It is arguable whether the pilocytic astrocytomas of the hypothalamus and optic chiasm observed by Meyerson and Sato et al., respectively, should be regarded as specific correlates of the NSS or, given their relatively frequent occurrence in children, mere coincidences [2].

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*Fig. 3. Ultrastructure of desmoplastic neuroepithelial tumor. A: Elongated astrocytic cell processes filled with intermediate filaments abut on bundles of collagen (arrow) – original magnification: ×1950. B: The surface of tumor cells is coated by discontinuous and sometimes redundant basal lamina (arrowheads). – Original magnification: ×1950.*
The patient taken care of and reported on by Andriola had a left parietal oligo-ependymoma ("mixed glioma"), histologically curious enough to be considered as a candidate of dysontogenetic neoplasm [1].

The case contributed by Burck et al. of an 8-year-old girl with unilateral skin atrophy, retroauricular "nodules", and a meningioma is particularly intriguing, since it attests to the patient’s propensity to develop multiple metachronous neoplasia [4]. Indeed, not only are meningiomas rare in young subjects, she also subsequently acquired an ameloblastoma. The occurrence may, therefore, represent either a phenocopy of NSS or a yet unidentified phakomatosis [4].

Described by Taratuto et al. as "Superficial Cerebral Astrocytoma Attached to Dura", a distinctive group of early infantile neoplasms has lately evolved into a broader concept of central nervous system tumors (DNETs) with versatile differentiation potential [14, 20, 23]. Paulus et al. demonstrated both glial and neuronal differentiation in two instances of an otherwise typical term “Desmoplastic Supratentorial Tumors of Infancy”, with which we agree [14]. As a matter of fact, reports on such tumors arising in atypical locations or ones not falling the original perception of an invariably indolent growth have been proliferating [19, 22]. Accordingly, some authorities put forward the idea of DNETs being the derivatives of pluripotential embryonic precursors, rather than lineage-committed cells [17]. Their ontogeny, therefore, is believed to involve both deregulated proliferation and erratic migration. Of note in this respect is that Levin et al. were able to visualize disorganized migration of cortical neurons in four of their cases [9]. Glioneuronal hamartomas are a common finding in pachygryia and hemimegalencephaly, both common correlates of the NSS [9, 18].

Prayson et al. provided evidence of enhanced astrocytic proliferation in gangliogiomas, a frequent focal lesion in dysplastic cortex [15]. Moreover, the glial component has been known to occasionally undergo malignant transformation [11]. Morioka called attention to the propensity of skin lesions in the NSS to undergo malignant transformation [12]. Indeed, basal cell carcinomas in affected patients tend to develop at a higher percentage and in younger age. Similarly, Van- denBerg warns that [DNETs] "should not be interpreted as benign or indolent." Specifically, that seems to hold true for tumors – like the one presented herein – harboring a small cell (PNET-like) moiety [23].

In summary, the focal neuropathological manifestations of the NSS are paradigmatic of phakomatoses in that affected cell types ostensibly escape supracellular structural organization [16, 24], and possess a ubiquitous propensity for neoplastic transformation [21]. The clinicopathological constellation in this case may also shed further light on the variegated natural history of DNETs.

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