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Testicular germ cell tumor showing concurrent PNET and neuroglial neoplasms with wide spectrum of grades.

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To the Editor:

In our recently published study, we presented primary and metastatic testicular germ cell tumors with neuroglial differentiation and neoplasms. We proposed a classification of “germ cell tumor with neuroglial neoplasm,” specifying which neuroglial tumor subtype is present, following the 2016 WHO Classification of Tumors of the Central Nervous System.1 We recently came upon a new case of a 24 year-old male with a primary testicular tumor. He presented to the emergency room with a one-week complaint of tender and painful enlarged testicle. An ultra-sound was performed, which revealed a solid and cystic mass replacing most of his testicle. Alpha-fetoprotein was elevated at 29.2 ng/mL (Normal range 0–10ng/mL) and HCG was negative (<1.0m[IU]/mL, Normal range 0–1m[IU]/mL). A radical orchiectomy was performed and a 5.7 × 4.5 × 3.6 cm tumor was identified. Histologically, the tumor was a malignant germ cell tumor composed of teratoma (90%) and yolk sac tumor (10%) with extensive areas of neuroglial differentiation. A post-surgical CT scan performed for staging revealed subcarinal and right hilar adenopathy measuring 3.7 cm, highly suspicious of metastases.

In contrast to our previously published cases, this tumor was characterized by a wide spectrum of glial neoplasia within different areas of the tumor, including low grade astrocytoma (WHO Grade I/II), anaplastic astrocytoma (WHO Grade III), and glioblastoma (WHO Grade IV). (Figure 1). The low-grade astrocytoma was composed of tumor cells with angulated nuclei and eosinophilic cytoplasm (Figure 1B). The anaplastic astrocytoma showed astrocytic cells with more pronounced nuclear atypia, higher cellularity and mitotic figures (Figure 1C and 1D). The glioblastoma component was identified due to the presence of marked nuclear atypia and pseudopalisading of tumor cells surrounding foci of tumor necrosis (Figure 1E). As in our previously published cases, the areas of neuroglial neoplasms were positive for GFAP and OLIG2 by immunohistochemistry.

In addition to neuroglial neoplasm of different grades, the current case showed a small focus of primitive neuroectodermal tumor (PNET). The PNET component consisted of a solid

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nodule with a uniform population of small cells, with round to oval hyperchromatic nuclei, scant cytoplasm, and rosettes arrangements (Figure 1F).2 This focus was negative for CD99 but showed nuclear staining for NKX2.2 and was negative for GFAP (Figure 1F insets). It has been previously demonstrated that the great majority of PNETs arising in teratomas do not show the same immunophenotype or share chromosome 22 abnormalities, and therefore negative immunostaining for CD99 is not unexpected.[2, 3] Tumor cells within the PNET component showed nuclear positivity for NKX2.2. While NKX2.2 is a helpful marker of PNETs, it is unclear whether it could be used to identify a PNET component in testicular tumors, as this has not been tested yet and because it has not been proven to be entirely specific for PNETs.4

In our previous series we described three patients in whom the metastatic tumor presented neuroglial neoplasm while the primary tumor showed PNET arising in a teratoma. However, none of these tumors had a concurrent PNET and a neuroglial neoplasm within the same tumor.1 We had hypothesized that the neuroglial neoplasm could be derived from the previous PNET. This current case is the first reported one with PNET and neuroglial neoplasms in the same tumor.

We have emphasized in our previous publication that, while neuroglial neoplasms meet the technical definition of somatic malignancy arising in teratomas, we believe it is most appropriate to report them as “neuroglial neoplasm” and not as “somatic malignancy,” based on our observation that their presence did not to alter the clinical outcome. In contrast to neuroglial neoplasms, PNETs are one of the most common somatic malignancies arising in teratomas.5 The PNET component in this case did not reach the size threshold of one low-power field (X4 objective, 5 mm in diameter field) to attain criteria for a somatic malignancy arising in a germ cell tumor and, therefore, this case was not reported as such. Furthermore, the presence of PNET gains clinical relevance when identified in metastatic sites because those present solely within the testicular tumor removed with radical orchiectomy bear and excellent prognosis.4 In summary, we report another example of neuroglial neoplasm arising in teratoma. In contrast to the previously published cases, this tumor presented a wide spectrum of grades and included a small focus of PNET, supporting the hypothesis that they are likely interrelated.

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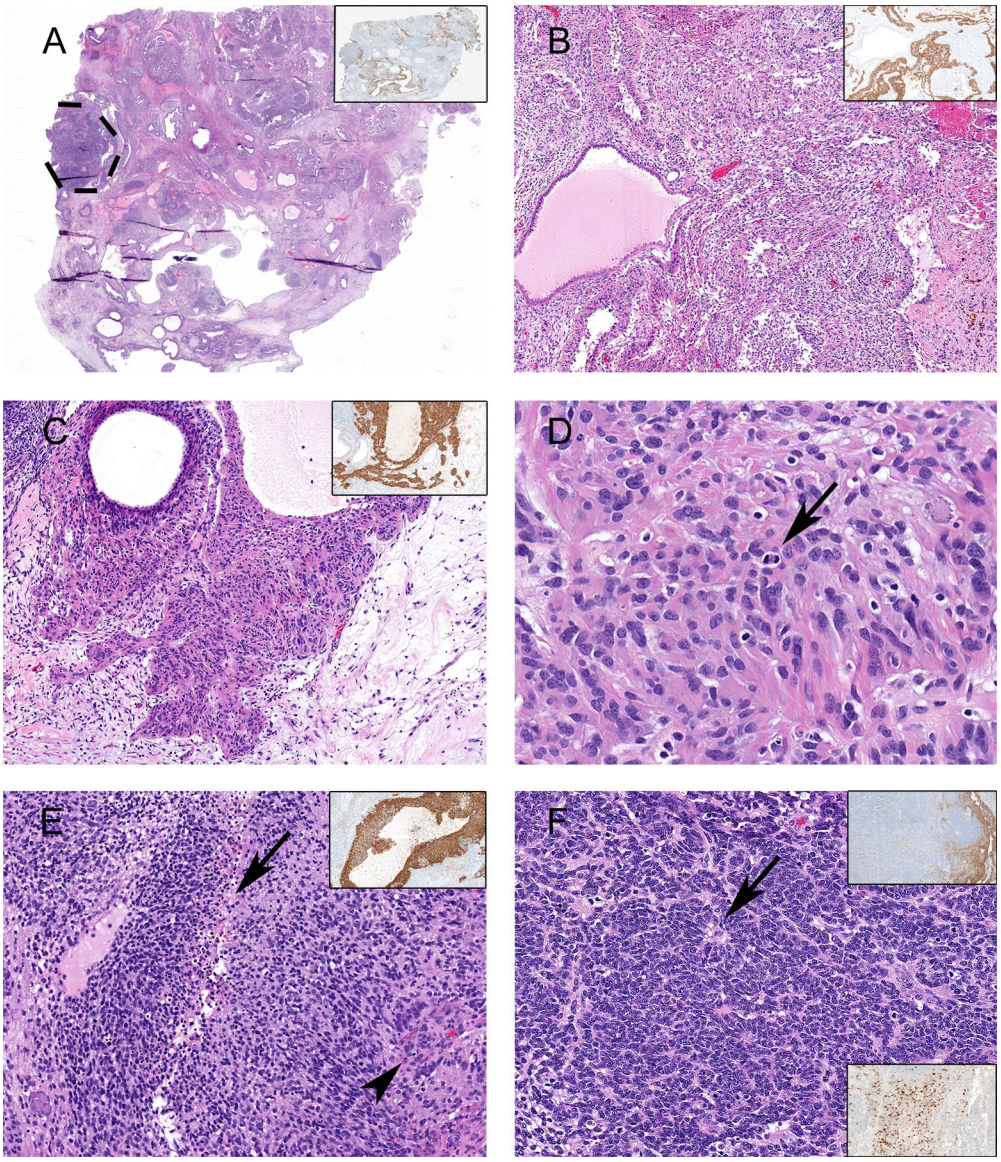

Figure 1.

A. Low power view of the tumor showing solid and cystic areas. The areas with neuroglial differentiation are positive for glial fibrillary acidic protein (GFAP; inset). The area inside the dotted line corresponds to a focus of primitive neuroectodermal tumor (PNET). ***B.*** Low-power view of a low-grade astrocytoma (WHO grade I/II) composed of spindle cells with eosinophilic processes. Inset shows positive immunostaining for GFAP within this area. ***C.*** Low power view of anaplastic astrocytoma (WHO grade III) characterized by a GFAP-positive (inset) spindle cell proliferation with fibrillary cytoplasm and mitotic activity. ***D.*** Higher power of "C" showing nuclear atypia, nuclear crowding and mitotic activity (arrow). ***E.*** Glioblastoma showing central necrosis (arrow) and vascular proliferation (arrow head). ***F.*** High-power view of primitive neuroectodermal tumor within dotted line of "A." There is a monomorphic population of cells with round and oval nuclei, scant cytoplasm and rosette

formation (arrow). This area is negative for GFAP (top right inset) but positive for NKX2.2 (bottom right inset).