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Diffuse Pediatric-type High-grade Glioma Arising in an Ovarian Mature Cystic Teratoma

Lena Elmuti, M.D.,
Departments of Pediatrics, University of Chicago, Chicago, Illinois

Julia Amundson, M.D.,
Departments of Surgery, University of Chicago, Chicago, Illinois

Elise Oberman, M.S.N.,
Departments of Pediatrics, University of Chicago, Chicago, Illinois

Aarti Kamat, M.D.,
Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

Laura Sedig, M.D.,
Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

Ricardo R. Lastra, M.D.,
Departments of Pathology, University of Chicago, Chicago, Illinois

Kenneth Aldape, M.D.,
National Cancer Institute, Bethesda, Maryland

Martha Quezado, M.D.,
National Cancer Institute, Bethesda, Maryland

Drew W. Pratt, M.D.,
National Cancer Institute, Bethesda, Maryland

Patrick J. Cimino, M.D., Ph.D.,
National Cancer Institute, Bethesda, Maryland

Zied Abdullaev, Ph.D.,
National Cancer Institute, Bethesda, Maryland

Peter Pytel, M.D.,
Departments of Pathology, University of Chicago, Chicago, Illinois

Mark A. Applebaum, M.D.,
Departments of Pediatrics, University of Chicago, Chicago, Illinois

Jennifer A. Bennett, M.D.
Departments of Pathology, University of Chicago, Chicago, Illinois

Address for correspondence: Jennifer A. Bennett, MD, Department of Pathology, University of Chicago, 5841 S Maryland Ave, MC 6101, Chicago, IL 60637. jabennett@bsd.uchicago.edu.

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Summary:

Immature neuroectodermal tissue can be found in the ovary as part of an immature teratoma or as part of a teratoma with malignant neuroectodermal transformation. Such lesions may closely resemble central nervous system tumors, but their biologic similarity is unclear. We describe an 18-yr-old female who presented with abdominal pain caused by an ovarian mass with widespread metastases. Histology showed a primitive, high-grade tumor arising in the background of a mature teratoma. The tumor was SOX10 positive, with focal expression of GFAP, S100, NSE, and synaptophysin. Molecular analysis demonstrated co-amplification of *PDGFRA* and *KIT*, alterations common in high-grade gliomas. By whole-genome methylation profiling, it clustered into the "diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass c" group. Despite progressing through 2 lines of chemotherapy with widespread metastatic disease, she achieved an excellent response to chemotherapy directed toward aggressive germ cell tumors. This case emphasizes the importance of immunohistochemical, genomic, and epigenetic analyses to accurately classify these exceedingly rare tumors and determine the optimal therapy.

Keywords

Ovary; Mature teratoma; Neuroectodermal tumor; Glioma; PDGFRA; Methylation

Ovarian tumors are common, occurring in both premenopausal and postmenopausal females. In premenopausal women, most neoplasms are epithelial, but a subset represent germ cell or sex cord-stromal tumors. Mature cystic teratomas are the most common type of germ cell tumor, accounting for 60% of all ovarian neoplasms in women <20 yr (1). These tumors average 6 cm in greatest dimension, but occasionally may be > 30 cm (2). Typically, they are unilateral, cystic, and filled with yellow-tan sebaceous material and hair (3). They are comprised of mature tissues from all 3 germ cell layers (ectoderm, endoderm, and mesoderm) including cartilage, bowel, thyroid, skin, hair, teeth, and neuroepithelium. While mature cystic teratomas are benign, somatic-type malignancy occurs in up to 2% of tumors, 80% of which are squamous cell carcinoma (4). Neuroectodermal tumors arising in a teratoma are exceedingly rare (4–8) and have not been extensively studied by immunohistochemical, genomic, and epigenetic analyses. Herein, we describe an 18-yr-old woman with a metastatic pediatric-type, high-grade glioma arising from a mature cystic teratoma of the ovary.

CASE REPORT

An 18-yr-old G0P0 woman with abdominal pain was found to have a 15.0 × 14.7 × 11.8 cm complex, multilobulated, calcified, and fatty mass of the left ovary on pelvic magnetic resonance imaging (MRI), radiologically consistent with a mature cystic teratoma. Additional imaging revealed para-aortic and retroperitoneal lymphadenopathy, and liver metastases. Serum neuron-specific enolase was > 1000 (normal <15) ng/mL. She underwent oophorectomy and lymphadenectomy at an outside institution and was diagnosed with "small cell neuroendocrine carcinoma." After 1 cycle of neuroendocrine-directed chemotherapy including carboplatin and etoposide, she was transferred to our institution for further care.

Internal pathology review of the left ovarian mass revealed a cellular, small round blue cell tumor growing in sheets, nests, trabeculae, and cords (Fig. 1). The cells had hyperchromatic ovoid nuclei with irregular contours, minimal cytoplasm, brisk mitoses, and conspicuous apoptotic bodies. In the corded and trabecular areas, the stroma was focally myxoid or hyalinized. Rosettes, pseudorosettes, primitive neural tubes, ganglion cells, and papillae were not identified. Extensive lymphovascular invasion was present, but necrosis was absent. Around the periphery of the tumor, hair shafts with an associated foreign body giant cell reaction were noted, consistent with a residual component of mature cystic teratoma. No other teratomatous elements were identified on the slides received for review (n = 4). Per report, several retroperitoneal lymph nodes were involved by tumor. By immunohistochemistry, the tumor was positive for SOX10, with focal expression of GFAP, S100, synaptophysin, and NSE, but negative for AE1/AE3, CAM5.2, chromogranin, CD99, FLI-1, desmin, myogenin, SALL4, CD30, and CD45 (Fig. 2). BRG-1 and INI-1 were retained, and p53 showed wild-type expression.

Next-generation sequencing using the University of Chicago Oncoplus panel, a DNA-based assay targeting 168 cancer-related genes (9), detected co-amplification of *PDGFRA* and *KIT* (Fig. 3A) as well as a *PDGFRA* rearrangement involving exon 9 and intron 10 (NM_006206.6). The tumor was microsatellite-stable with a tumor mutational burden of 2.9 mutations per megabase, and no fusions were detected on a 1005-gene RNA sequencing panel. Whole-genome methylation analysis at the National Institutes of Health/National Cancer Institute showed that the tumor classified as “glioblastoma, *IDH*-wildtype, subclass midline” using version 11 of the central nervous system (CNS) classifier (10). Analysis using version 12 of the CNS classifier placed the tumor into “diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass c,” which is an updated class in the new version of the classifier. The NCI-Bethesda classifier also grouped the tumor as a “diffuse pediatric-type high-grade glioma, H3-wildtype, and *IDH*-wildtype, subclass RTK1 with a high confidence score of 1.0.” Uniform manifold approximation and projection analysis placed this tumor within the “diffuse pediatric-type high-grade glioma, RTK1c subtype” group (Fig. 3B).

After confirmation of a tumor with molecular and epigenetic features of a glioma arising from a germ cell tumor and decreased retroperitoneal lymphadenopathy following 1 cycle of carboplatin and etoposide, she was treated per the Children’s Oncology Group protocol ACNS2021, a phase 2 study for patients with localized nongerminomatous CNS germ cell tumors. Chemotherapy included cycles of carboplatin and etoposide alternating with ifosfamide and etoposide. Despite initial pain reduction and decreasing retroperitoneal lymphadenopathy, imaging after 4 cycles demonstrated new pulmonary nodules. Subsequent lung biopsy was positive for a malignant small round blue cell tumor, consistent with metastasis from the known ovarian primary. She then received 1 cycle of glioma-directed therapy (bevacizumab and lomustine) (11), but rapidly developed a malignant ureteral obstruction with hydronephrosis, as well as worsening of her lymphadenopathy and bony metastases. Relapsed germ cell tumor-directed therapy was then initiated which included paclitaxel, ifosfamide, and cisplatin (TIP) (12). After 4 cycles, she achieved complete metabolic remission on positron emission tomography scan; however, subsequent liver and retroperitoneal lymph node biopsies demonstrated viable disease, so she received an

additional cycle of TIP chemotherapy followed by 35 Gy of retroperitoneal radiation. Most recently, she developed worsening peripheral neuropathy with focal muscle weakness and sensory deficits on her right side concerning for disease progression. Brain and spine MRI revealed multifocal vertebral body lesions, consistent with treated metastases without evidence of disease progression or cord compression. At last follow-up, she is alive with the disease, 12 mo after initial diagnosis.

DISCUSSION

In 1982, Aguirre and Scully (5) reported the first series of neuroectodermal tumors arising in the ovary. In this study, they described 5 ovarian tumors that closely resembled CNS neoplasms, 2 of which contained residual foci of mature teratoma. All were comprised of undifferentiated pleomorphic cells, with 4 showing glial differentiation, 2 having ependymal differentiation, 1 with a medulloepithelioma-like appearance, and 1 compatible with neuroblastoma. As these features resembled CNS primitive neuroectodermal tumors, they proposed using a similar terminology to classify the ovarian neoplasms. Furthermore, as the majority (or entirety) of these tumors were comprised of malignant neuroectoderm, they advocated that these tumors should be placed in a separate category from immature teratomas, recommending they should be classified as a type of monodermal teratoma.

A subsequent series evaluated 25 ovarian neuroectodermal tumors and divided them into 3 groups based on their morphologic features: differentiated (primarily ependymomas), primitive/primitive neuroectodermal tumors (those formerly classified as medulloblastoma, neuroblastoma, medulloepithelioma, ependymoblastoma, and now referred to as “embryonal tumors” in the CNS), and anaplastic (glioblastoma) (6). Patients in the differentiated category were older (mean: 30 yr) and tumors were not associated with a teratoma, while those in the primitive and anaplastic groups were younger (mean: 23 and 16 yr, respectively) and tumors often exhibited a residual teratoma (58% and 100%, respectively). In all categories, patients with stage I disease had a favorable outcome (aside from 1 patient with an anaplastic tumor who died from disease 2 yr after diagnosis), whereas all with stage III tumors were either alive with disease or died of disease at last follow-up. Of note, as the term “primitive neuroectodermal tumors” has since been eliminated from the CNS nomenclature and is no longer used to describe Ewing sarcoma in the soft tissue, it has been proposed to classify these tumors in the gynecologic and genitourinary tracts as “embryonic-type neuroectodermal tumor” (13). However, as the preferred terminology in the most recent WHO Classification of Female Genital Tumors is “neuroectodermal tumor,” this verbiage will be used in the remainder of the discussion (14).

The immunohistochemical profile of neuroectodermal tumors arising in the gynecologic tract and peritoneum is often dependent on the type of CNS neoplasm it recapitulates. Usually, those resembling glial tumors are GFAP positive (may be focal), with embryonal tumors showing variable expression, and neuronal tumors being negative (4,6–8). In contrast, both embryonal and neuronal tumors are typically positive for neuroendocrine markers, while glial neoplasms show variable expression (4,7,8). Both glial and embryonal tumors may be positive for FLI-1, CD99, and S100, which have not been studied in neuronal neoplasms (7). This patient’s tumor focally expressed GFAP and S100, as well

as neuroendocrine markers (synaptophysin and NSE), which would be expected in a glial neoplasm. In addition, it was diffusely positive for SOX10, an oligodendrocyte precursor marker and chromatin modifier that is overexpressed in receptor tyrosine kinase 1 (RTK1) adult glioblastomas (15).

Although the immunohistochemical profiles are similar between CNS neoplasms and neuroectodermal tumors arising in the gynecologic tract, the molecular underpinnings of the latter have yet to be elucidated. In the CNS, oligodendrogliomas are characterized by co-deletion of chromosomes 1p and 19q. Although one oligodendroglioma arising in an ovarian teratoma showed loss of heterozygosity for chromosomes 19q13 and 10q, no copy number alterations were noted in chromosome 1p (16). Other studies investigated for *IDH1/IDH2* mutations in astrocytomas, *C19MC* amplification in embryonal tumors, and *BRAF V600E* mutations in pilocytic astrocytomas, but such alterations were not identified (4,8). Likewise, these genomic alterations were not detected in neuroectodermal tumors arising in teratomas from nongynecologic sites (17,18).

This contrasts with the tumor described here which showed co-amplification of *PDGFRA* and *KIT*, along with a *PDGFRA* rearrangement, all of which are common in gliomas (19–21). By whole-genome methylation studies, this tumor clustered in the same methylation class as diffuse pediatric-type high-grade glioma, an aggressive pediatric glioma characterized by the lack of H3 and *IDH* mutations. Three subtypes have been identified based on genome-wide DNA methylation profiling and analysis of gene expression data, which include MYCN (*MYCN/MYC* amplification), RTK1 (*PDGFRA* amplification), and RTK2 (*EGFR* amplification) (20). Morphologically, they exhibit glial and/or primitive differentiation, with the RTK1 and RTK2 subtypes often showing focal expression of GFAP or OLIG2 (22). This was also true for this patient's tumor as morphologically it had a primitive appearance and focally expressed GFAP (not tested for OLIG2).

The biologic similarity with a high-grade pediatric-type glioma likely accounts for the clinically aggressive behavior of this tumor. However, identification of this specific molecular and epigenetic profile raises questions about the optimal approach to treating these patients, especially given that treatment for germ cell tumors with non-germ cell components has not been defined, and consensus opinion suggests therapy directed toward both morphologies may be indicated (23). Platinum-based agents are a cornerstone for both gliomas and germ cell tumors and this patient had an initial partial response to platinum-based therapy (24). CNS-directed therapy was not of benefit to her as second-line therapy, though this combination has only been of modest utility for patients with standard gliomas (11). First-line therapy for germ cell tumors often consists of bleomycin in addition to etoposide and carboplatin (25), though it is unclear if substituting bleomycin for ifosfamide would have been more effective initially as the latter was part of the clinically beneficial third-line TIP therapy.

A brief discussion on the differential diagnosis of this tumor is merited. Although the presence of residual teratomatous elements highly favored a somatic-type malignancy arising in a mature teratoma, the possibility of an incidental, unassociated teratoma could not be entirely excluded. Other entities that should be considered include small cell carcinoma

of the ovary, hypercalcemic type, Ewing/Ewing-like sarcoma, small cell neuroendocrine carcinoma, embryonal rhabdomyosarcoma, embryonal carcinoma, melanoma, lymphoma, and undifferentiated carcinoma; however, a thorough immunohistochemical, and if necessary, molecular evaluation would be able to exclude these morphologic mimickers.

In summary, we describe the first example of a malignant neuroectodermal tumor arising in a teratoma with a molecular and epigenetic profile that parallels a specific CNS neoplasm. This case emphasizes the need for a comprehensive immunohistochemical, genomic, and epigenetic evaluation to accurately classify these exceedingly rare tumors. These ancillary techniques enabled rational, pathologically directed therapeutic approaches, resulting in significant disease response to therapy and clinical benefit for the patient. This affirms efforts to centralize clinical and molecular data collection of rare tumors to better understand their pathobiology and determine optimal therapy.

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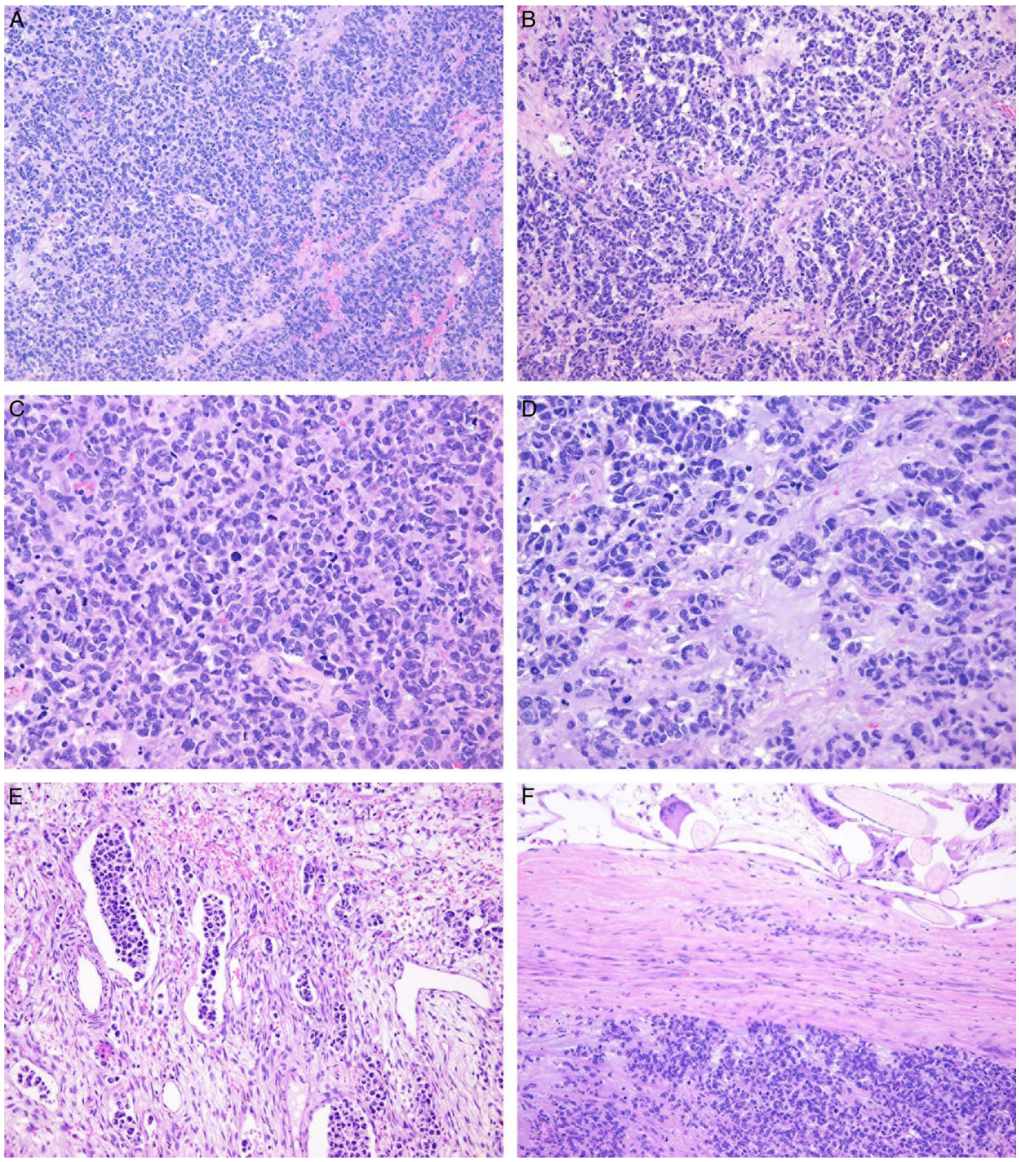

FIG. 1.

The tumor showed multiple architectural patterns including sheets (A) and cords (B) and was comprised of small round blue cells with brisk mitoses (C). Myxoid stroma was focally noted (D), while lymphovascular invasion was extensive (E). Hair shafts, with an associated foreign body giant cell reaction, were present at the periphery (F), consistent with residual teratoma.

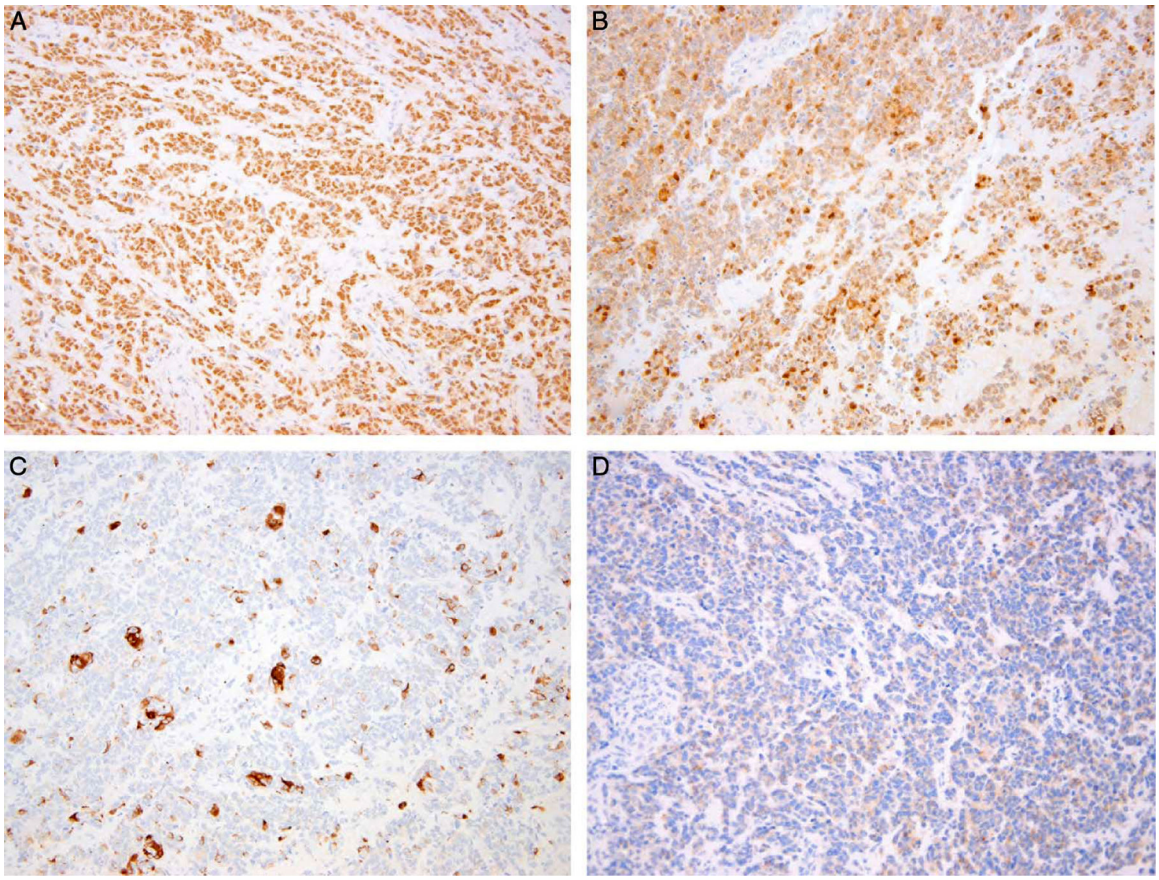

FIG. 2.

The tumor was diffusely positive for SOX10 (A), with focal expression of S100 (B), GFAP (C), and synaptophysin (D).

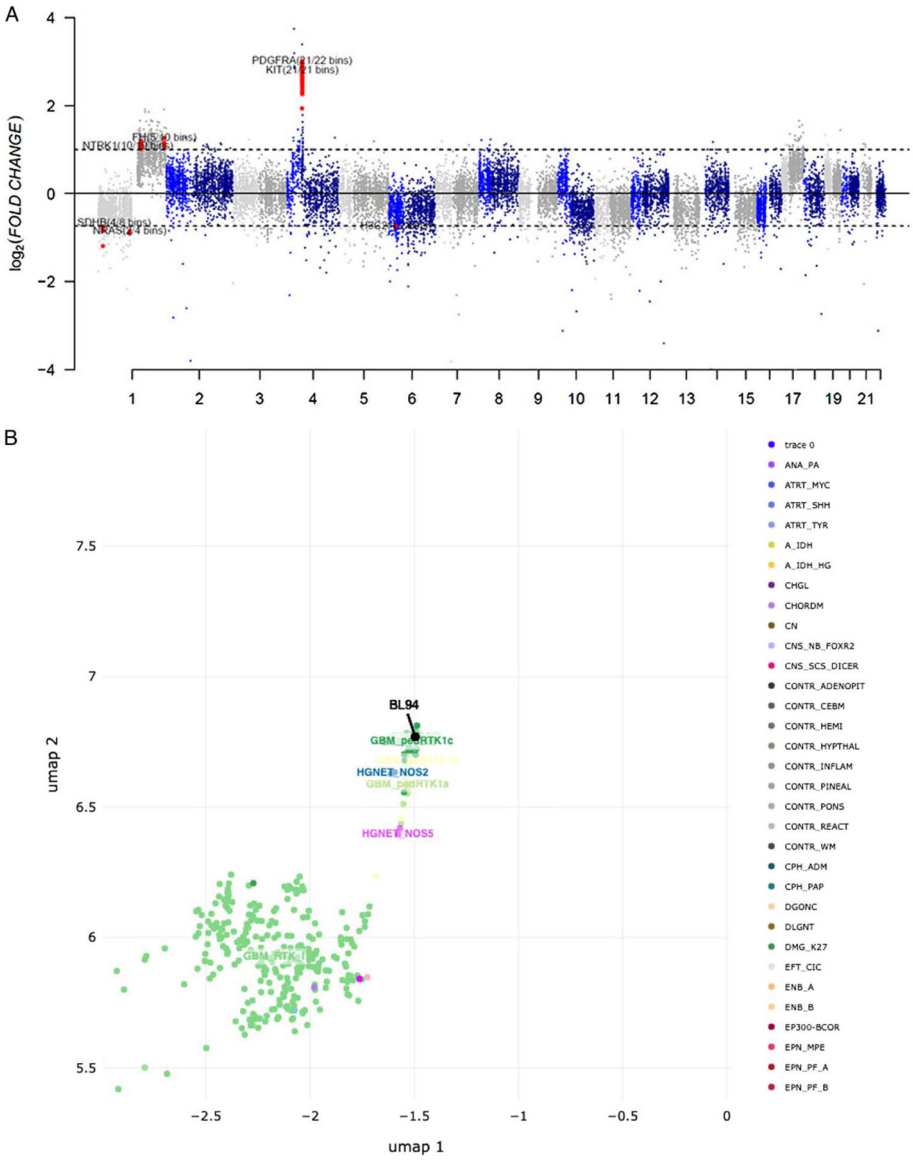

FIG. 3.

Copy number analysis revealed co-amplification of *PDGFRA* and *KIT* (A). Uniform manifold approximation and projection embedding placed the tumor (“BL94,” black circle) into the methylation class “diffuse pediatric-type high-grade glioma, RTK1c subtype” shown in green as “GBM_ped RTK1c” (B).