Malignant intracerebral nerve sheath tumor in a patient with Noonan syndrome: illustrative case

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BACKGROUND Malignant peripheral nerve sheath tumors (MPNSTs) within the neuroaxis are rare, usually arising from peripheral and cranial nerves. Even more scarce are cranial subclassifications of MPNSTs termed “malignant intracerebral nerve sheath tumors” (MINSTs). These tumors are aggressive, with a strong tendency for metastasis. With this presentation, alongside resistance to adjunctive therapy, complete excision is the mainstay of treatment, although it is often insufficient, resulting in a high rate of mortality.

OBSERVATIONS The authors report the case of an adult patient with a history of Noonan syndrome (NS) presenting with slowly progressive rightsided hemiparesis and right-sided focal motor seizures. Despite initial imaging and histology suggesting a left frontal lobe high-grade intrinsic tumor typical of a glioblastoma, subsequent molecular analysis confirmed a diagnosis of MINST. The patient’s neurological condition improved after gross-total resection and adjuvant chemo-radiation; he remains on follow-up.

LESSONS MINSTs are rare neoplasms with a poor prognosis; management options are limited, with surgery being the cornerstone of treatment. Reports on rare tumors such as this will increase awareness of this particular pathology and disclose clinical experience. In this case, the authors were unable to establish a definite cause-and-effect relation between NS and MINST. Nevertheless, it remains the first reported case in the literature.

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KEYWORDS malignant peripheral nerve sheath tumor; malignant intracerebral nerve sheath tumor; malignant schwannoma; frontal lobe; intraparenchymal

Malignant peripheral nerve sheath tumors (MPNSTs) occurring within the neuroaxis are rare, usually arising from peripheral and cranial nerves. Even more unusual are subclassifications evolving from the brain parenchyma, widely known as malignant intracerebral nerve sheath tumors (MINSTs). Because of a propensity for fierce regional infiltration and complex metastatic capability, these tumors are considered aggressive. With this presentation, and a resistance to adjunctive treatment, gross-total resection (GTR) is the mainstay of management; however, recurrence is often considered inevitable, particularly in cases in which GTR is not achieved. Therefore, MINSTs are associated with a high rate of mortality and poor overall survival; notwithstanding these outcomes, survival figures differ in the literature, particularly at 1 and 5 years after diagnosis, highlighting the need for a review of the literature. Here, we present a rare case of an MINST in the frontal lobe that was initially suspected to be a high-grade glioma, was initially managed with GTR,

ABBREVIATIONS CNS = central nervous system; GFAP = glial fibrillary acidic protein; GTR = gross-total resection; LL = lower limb; MAPK = mitogen-activated protein kinase; MINST = malignant intracerebral nerve sheath tumor; MPNST = malignant peripheral nerve sheath tumor; MRI = magnetic resonance imaging; NF-1 = neurofibromatosis-1; NS = Noonan syndrome; TERT = telomerase reverse transcriptase; UL = upper limb; WHO = World Health Organization.

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and has since completed adjuvant treatment. We have also undertaken a review of the medical literature with the aim to present the latest diagnostic and therapeutic developments on this rare entity.

**Illustrative Case**

A 49-year-old, left-handed man with a background of Noonan syndrome (NS) and who had undergone surgery early in childhood for congenital pulmonary stenosis presented to our neurosurgical department with a 7-month history of progressive right-sided hemiparesis and, more acutely, daily focal motor seizures of the right arm and leg.

Neurological examination elicited normal cranial nerve function, including visual fields with no neglect and normal fundoscopy. Motor examination demonstrated normal power and tone in the left upper limb (UL) and lower limb (LL), with a pyramidal catch in the right UL and obvious pyramidal weakness in the right LL (hip flexion 3/5, extension 4/5, knee flexion 4/5, extension 4/5, dorsiflexion 2/5, plantarflexion 4/5) with symmetrical, pathologically brisk reflexes. There was reduced sensation down the right arm, leg, and torso to all modalities. His performance status was 2 (according to the World Health Organization [WHO] classification).

Initial magnetic resonance imaging (MRI) in September 2020 demonstrated a heterogeneously enhancing lesion with necrosis, suggestive of a high-grade glioma (Fig. 1). Thus, the patient was listed for a neuronavigated craniotomy for debulking of the lesion after multidisciplinary team review.

Intraoperatively, a linear incision was made and a posterior frontal craniotomy was performed using neuronavigation. An encapsulated tumor was subsequently found and macroscopically excised, achieving GTR. Postoperatively, the patient had a Glasgow Coma Scale score of 15, with an improving right-sided weakness (UL 2/5, LL 3/5). Of note, the postoperative MRI and planning MRI for radiotherapy subsequently demonstrated contrast enhancement within the caudal aspect of the surgical bed (Fig. 2), deemed later to be postsurgical inflammatory changes.

Initial histology reports noted an unusual high-grade neoplasm with a predominantly spindle cell appearance. Further immunostaining revealed a tumor negative for IDH1 (R132H) and BRAF (V600E) mutation with ATRX retention and a Ki-67 labeling index of 20% to 30% (complete histomolecular analysis is shown in Table 1). Histological appearances revealed an unusually high-grade, intrinsic central nervous system (CNS) tumor, with a differential diagnosis including gliosarcoma (with a desmoplastic-appearing glial component that also included abnormal ganglion/ neuronal cells) and anaplastic pleomorphic xanthoastrocytoma (Fig. 3). Sanger sequencing further showed the tissue to be IDH1-R132 and IDH2-R172 wild type, with no mutations in the telomerase reverse transcriptase (TERT) promoter or histone H3F3A genes. The DKFZ (German Cancer Research Center, Heidelberg) sarcoma methylation classifier.

**TABLE 1. Initial immunohistochemistry and molecular pathology analysis results**

| Molecular/Immunohistochemical Analysis | Result |
|---------------------------------------|--------|
| IDH (R132H) IHC                       | Negative |
| IDH1/IDH2 sequencing                  | No mutation |
| FISH for 1p/19q codeletion             | Not performed |
| ATRX                                 | Retained in neoplastic cell population |
| MGMT promoter status                  | Unmethylated |
| TERT (228, 250)                       | No mutation |
| Histone H3F3A (K27, G34)              | No mutation |
| BRAF (V600E) (IHC/sequencing)         | Negative |
| H3K27me3                              | Loss of nuclear expression |
| NFP                                  | Highlights abnormal neuronal population w/ entrapped axons in keeping w/ an infiltrative growth pattern |
| GFAP                                 | Patchy positive staining |
| P53                                  | A small population of scattered weakly positive cells |
| STAT6                                | Negative |
| Ki-67 proliferation                   | 20%–30% |

**FIG. 1.** Preoperative T1- and T2-weighted MRI demonstrating a contrast-enhancing left posterior frontal lesion with necrotic features and surrounding edema. **A:** Preoperative sagittal T2-weighted MRI. **B:** Preoperative transverse T2-weighted MRI. **C:** Postoperative transverse T1-weighted MRI. **D:** Postoperative sagittal T1-weighted MRI.

**FIG. 2.** Postoperative transverse (**left**) and sagittal (**right**) T1-weighted MRI demonstrating complete resection of the left paramedian posterior frontal tumor.

**ATRX = ATRX gene; BRAF = B-Raf proto-oncogene; FISH = fluorescent in-situ hybridization; H3K27me3 = histone 3 lysine 27 trimethylation; IDH1 = isocitrate dehydrogenase; IHC = immunohistochemistry; MGMT = O6-methylguanine DNA methyltransferase; NFP = neurofilament protein; STAT6 = signal transducer and activator of transcription 6.**
of occurrence predominantly involve peripheral nerves, specifically in the limbs and trunk, although cranial nerves can also be sites of origin.\textsuperscript{7,8} Spontaneous MPNSTs are scarce, with an incidence of 0.1/100,000 persons per year.\textsuperscript{9} MPNSTs can be either extra- or intracranial, with the latter type being subclassified into extraaxial and intraparenchymal tumors. Serious consideration was given to this case because intracranial, intraparenchymal MPNSTs are extraordinarily rare, and reports in the international literature remain scarce. Because of the complex anatomo-topographic deployment inherent to their character, these neoplasms are generally known as MINSTs.\textsuperscript{10} Unfortunately, this subclassification is noted to have a penchant for a moderate to poor response to radiation and chemotherapy, with GTR with wide margins considered the cornerstone of management.\textsuperscript{2,11} However, postoperative recurrence and distant metastasis remain likely as a result of the aggressive nature of these tumors;\textsuperscript{15} indeed, the 1-year overall survival rate stands at 33%.\textsuperscript{12} Therefore, adjunctive radical radiotherapy is often integrated in the portfolio of mainstay therapy.

In the case presented here, there is a background of NS, an autosomal dominant condition with a variable phenotype, in which 50\% of cases are due to a germline “gain of function” mutation of the \textit{PTPN11} gene; this particular gene is responsible for encoding the nonreceptor protein tyrosine phosphatase SHP2, positively controlling the RAS function within the RAS–mitogen-activated protein kinase (MAPK) signaling pathway.\textsuperscript{13,14}

Considering the nature of the RAS-MAPK pathway and its role in oncogenesis, patients with certain mutations (so-called RASopathies), and thereby NS, are at an increased risk of certain cancers. Somatic mutations of \textit{PTPN11} have been reported as being present in 35\% of persons with juvenile myelomonocytic leukemia, alongside other hematological malignancies and solid organ tumors, such as lung and colon cancer and neuroblastoma.\textsuperscript{15,16} Overall, individuals with NS have an estimated cancer risk of 4\% by 20 years old.

Currently, limited evidence details the relationship between CNS tumors and NS, with most articles providing case reports of pediatric glial tumors. A case report and literature review of these tumors occurring alongside NS by Lodi and colleagues in 2020 demonstrated that most cases occurred in the pediatric population and were dysembryoplastic neuroepithelial tumors.\textsuperscript{17} Adult cases and primary brain tumor reports remain extremely scarce.

The significance of NS preexisting a diagnosis of MINST is unclear in the literature; indeed, should the relationship prove to be causal, our case would provide the first instance of MINST reported in an adult with NS. However, because of the lack of evidence in the medical literature, we tend to remain cautious on this subject.

Diagnosis

As illustrated by this case, preoperative diagnosis can be difficult, and the lesion’s appearance can be indistinguishable from high-grade glioma on imaging.\textsuperscript{5} MR spectroscopy showing a high choline peak without creatine and N-acetyl aspartate resonance has been suggested to differentiate between a glial and nonglial tumor, but awareness and a degree of suspicion are required.\textsuperscript{19} The latter study was not made available for our case because local institutional guidelines are not yet set in that direction. From a histological standpoint, the cellular origin of these neoplasms is still unknown; however, some groups have suggested Schwann cells of perivascular nerves or pluripotent mesenchymal cells as plausible sources.\textsuperscript{20}

Important diagnostic markers include the S100 protein, useful to demarcate nerve sheath tumors from tertiary soft tissue neoplasms;
| Case No. | Authors & Yr | Age (yrs) at Diagnosis | Gender | Laterality | Location | Surgical Procedure | Postop Therapy | Recurrence (mos) | FU (mos) | Survival at Last FU |
|----------|--------------|------------------------|--------|------------|----------|---------------------|----------------|------------------|---------|---------------------|
| 1        | Current study | 49                     | M      | Lt         | Frontal  | GTR                 | RT & CT        | —                | Ongoing (6 at time of writing) | Alive    |
| 2        | Le Fèvre et al., 2016 | 68             | F      | Lt         | Fronto-temporal | STR              | RT         | 7                | 15       | Dead                |
| 3        | Le Fèvre et al., 2016 | 47             | F      | Rt         | Frontal  | GTR                 | RT           | 6, 10, 13       | 20       | Alive               |
| 4        | Smith et al., 2014 | 26             | M      | —          | Bifrontal | STR                | —            | 1                | 12       | Dead                |
| 5        | Lee et al., 2013 | 13             | M      | Rt         | Frontal  | Resection (not specified) | RT | 50, 54, 60 | 77       | Alive               |
| 6        | Shweikeh et al., 2013 | 18             | M      | Rt         | Fronto-parietal | GTR            | RT         | 44                | 52       | Dead                |
| 7        | Gong et al., 2012 | 55             | F      | Lt         | Cerebellopontine angle | Resection (not specified) | — | No          | 5        | Alive               |
| 8        | van den Munckhof et al., 2011 | 6              | F      | Rt         | Fronto-parietal | GTR            | RT & CT    | 15                | 48       | Alive               |
| 9        | Ellis et al., 2011 | 75             | F      | Lt         | Frontal  | GTR                 | RT           | No               | 6        | Alive               |
| 10       | Barnard et al., 2011 | 15             | M      | —          | Posterior fossa | Not specified   | — | —            | Lost to FU | —                   |
| 11       | Oztanir et al., 2009 | 5              | M      | Rt         | Fronto-temporo-parietal | STR | — | 1.5            | Dead     |
| 12       | Scheithauer et al., 2009 | 69             | M      | Rt         | Frontal  | No treatment        | — | —            | 4        | Dead                |
| 13       | Scheithauer et al., 2009 | 26             | M      | —          | Posterior fossa | Not specified | — | —            | Lost to FU | —                   |
| 14       | Scheithauer et al., 2009 | 41             | M      | —          | Posterior fossa | Resection (not specified) | RT | — | 5        | Dead                |
| 15       | Kozic et al., 2008 | 39             | M      | Lt         | Pontine  | Biopsy              | — | —            | Not Specified | —                   |
| 16       | De Cauwer et al., 2007 | 68             | F      | Lt         | Parieto-frontal (rolandic area) | GTR | RT | 5       | 5        | Dead                |
| 17       | Maiuri et al., 2004 | 36             | M      | —          | Cerebellar vermis | GTR | RT | 6       | 8        | Dead                |
| 18       | Beauchesne et al., 2004 | 35             | M      | Rt         | Cerebral peduncle | Biopsy | RT & CT | 17       | 29       | Dead                |
| 19       | Bomstein-Quevedo et al., 2003 | 3              | M      | Rt         | Parieto-occipital | STR | — | 0.33        | Dead     |
| 20       | Takahashi et al., 2000 | 57             | M      | Rt         | Lateral ventricle | GTR | RT & CT | — | 4        | Dead                |
| 21       | Tanaka et al., 2000 | 4              | F      | Rt         | Parieto-occipital | GTR | — | 19       | Alive               |
| 22       | Sharma et al., 1998 | 8              | F      | Rt         | Temporal | GTR               | — | No | 17       | Alive               |
| 23       | Jung et al., 1996 | 40             | M      | Rt         | Lateral ventricle | GTR | RT | 8       | 8        | Dead                |
| 24       | Singh et al., 1993 | 61             | F      | Rt         | Cerebellar | GTR | RT | 10       | 18       | Dead                |
| 25       | Stefanko et al., 1986 | 15             | M      | Lt         | Parieto-occipital | GTR | RT & CT | 5, 8     | 9        | Dead                |
| 26       | Bruner & Armstrong, 1984 | 18             | M      | —          | Bifrontal | GTR | — | 24, 48, 66 | 66       | Alive               |

CT = chemotherapy; FU = follow-up; RT = radiotherapy; STR = subtotal resection.
loss of nuclear H3K27me3 expression, seen in most MPNSTs,\textsuperscript{7,21} negative glial fibrillary acidic protein (GFAP) expression, which helps exclude desmoplastic astrocytoma, glioblastoma, and gliosarcoma; and negative synaptophysin and neurofilament protein, which reliably distinguish MINSTs from desmoplastic ganglioglioma.\textsuperscript{3,22} Other differential diagnoses include other tumors such as rhabdomyosarcoma, gastrointestinal stromal tumor, and meningioma.\textsuperscript{33}

In our case, S100 positivity coexisting with patchy GFAP expression proved challenging and certainly delayed diagnosis. Additionally, as mentioned above, this tumor initially appeared similar to a glioblastoma on imaging. Histologically, this was thought not to be the immediate case because of certain morphological clues such as the appearance of a malignant tumor with a mesenchymal appearance, alongside the aforementioned absent GFAP expression. Gliosarcoma was indeed considered; however, it was deemed unlikely because of the lack of biphasic architecture (only malignant mesenchymal with no high-grade glioma component). A tumor falling within the hemangiopericytoma/extravascular fibrous tumor spectrum was also excluded based on STAT6 immunohistochemistry and DNA methylation profiling. The latter also helped to rule out a diagnosis of anaplastic pleomorphic xanthoastrocytoma. Further analysis to differentiate between MINST and other high-grade tumors, such as SOX10 and reticulin staining, could have been conducted; however, local guidelines favor the reliability of H3K27me3 and DNA methylation profiling from a diagnostic perspective. Local capabilities of analyzing Olig2 expression were not available to us at the time of diagnosis. To that end, the histological and immunohistochemical profile of this tumor did not fit with any known high-grade glioma or any other specific entity recognized by the current WHO classification of CNS tumors.

Treatment and Follow-up

Surgical management of intracranial MPNSTs is technically complex because of frequent involvement with a cranial nerve. Indeed, Patankar et al. described the challenges associated with resection of an MPNST in the middle cranial fossa and its close involvement with the facial nerve and geniculate ganglion, resulting in a postoperative facial palsy.\textsuperscript{10} Scheithauer and colleagues also reported a similar finding.\textsuperscript{9} In the case discussed within this report, no cranial nerves were involved. Of note, this is not surprising because intraparenchymal MINSTs arise from the brain parenchyma, and as a result cranial nerve involvement remains a less common finding in similar cases.\textsuperscript{23} In terms of adjuvant therapy, radiotherapy remains the most favored approach; however, local guidelines favor the reliability of H3K27me3 and DNA methylation profiling from a diagnostic perspective. Local capabilities of analyzing Olig2 expression were not available to us at the time of diagnosis. To that end, the histological and immunohistochemical profile of this tumor did not fit with any known high-grade glioma or any other specific entity recognized by the current WHO classification of CNS tumors.

Lessons

Multiple lessons can be learned from this case, particularly regarding diagnosis and management. (1) There have been few reports of MINSTs in the literature, with only 25 reported since 1984; none of these cases had a background of NS (Table 2). As a result, it is hypothesized that the rarity of malignant intraparenchymal peripheral nerve sheath tumors brings about a lack of evidence on the best management of these lesions, and although there is insufficient evidence to establish a proper cause-and-effect relation between the two entities, it cannot be fully discarded considering NS’s oncogenic capability. (2) MINST can mimic glioblastoma clinically, radiologically, and, to some extent, even histopathologically. This possibility highlights the importance of reliable immunohistochemistry and institutional experience with these rare neoplasms. (3) With surgery being the mainstay treatment, postoperative treatment remains surrogate to the clinical evolution of MINSTs. However, the scarce number of patients makes retrospective analytical work and prospective studies hardly feasible; thus, there is a lack of consensus regarding the adequate postoperative and/or adjuvant management of these tumors, although it seems that radiotherapy has a clearer therapeutic role than chemotherapy.

We believe this case to be the 26th reported case of MINST in the available literature; additionally, to our knowledge, this is the first reported case of MINST in an adult patient with a background of NS. However, as pointed out above, the lack of data in the medical literature makes it difficult to discern between a complex causal relation and a mere incidental finding. Finally, we suggest that an international registry focusing on diagnostics, applied treatments, and therapeutic outcome should be considered with the aim of achieving a wider consensus in the management of these rare and complex entities.

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Conception and design: Sinclair, Allison, Shumon, Surash. Acquisition of data: Shumon, Allison. Analysis and interpretation of data: Sinclair, Shumon, Joshi, Quaegebeur. Drafting the article: Sinclair, Allison, Quaegebeur. Critical revising the article: Sinclair, Shumon, Quaegebeur. Reviewed submitted version of the article: Sinclair, Allison, Shumon, Joshi, Quaegebeur. All authors had access to the data and approved the final version of the manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sinclair. Administrative/technical/material support: Sinclair, Shumon, Joshi. Study supervision: Sinclair, Surash.

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