Intracranial desmoplastic small round cell tumor presenting as a suprasellar mass

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Desmoplastic small round cell tumors (DSRCTs) are rare, aggressive neoplasms that typically arise from abdominal and pelvic peritoneum in young adults. Other primary sites are uncommon, and an intracranial origin is exceptionally rare. Here the authors report the first case of a DSRCT presenting as a primary suprasellar tumor causing panhypopituitarism and severe bitemporal hemianopia in a young man. Macroscopic debulking of the tumor was undertaken, and histology revealed features of DSRCT. Reverse transcription polymerase chain reaction confirmed the presence of Ewing’s sarcoma–Wilms tumor 1 (EWS-WT1) gene rearrangement specific to DSRCT. Postoperative whole-body imaging showed no primary malignancy elsewhere. The tumor recurred 4 months after surgery, and this was followed by cervical and mediastinal lymph node metastases. The patient died 20 months after initial presentation of rapidly progressive disease. DSRCTs should be included in the differential diagnosis of an unusual suprasellar mass in young adults. Early diagnosis is essential, and once the tumor is identified histologically, gross-total resection and radical postoperative treatment involving radiotherapy, chemotherapy, and close surveillance are required because of the lesion’s potential for rapidly progressive malignancy.

http://thejns.org/doi/abs/10.3171/2014.10.JNS132490

KEY WORDS desmoplastic small round cell tumor; suprasellar mass; EWS-WT1 gene fusion; intracranial malignant tumor; oncology

Desmoplastic small round cell tumors (DSRCTs) are rare, aggressive neoplasms that have an aggressive clinical course. Despite multiple modalities of treatment, these tumors remain incurable and have poor long-term survival rates. They were first described in 1989 by Gerald and Rosai.3 These tumors are more common in males and usually present in adolescence or early adulthood. There are no reliable biomarkers or specific radiological signs for their diagnosis; however, recent advances in molecular biology and immunohistochemistry allow reliable diagnosis through examination of a biopsy specimen in most cases. Cytogenetic analysis in DSRCTs has shown a specific chromosomal abnormality, t(11;22)(p13;q12), as a result of gene translocation and rearrangement of the genes for Ewing’s sarcoma (EWS) and Wilms tumor 1 (WT1). The gene fusion of EWS-WT1 is described to be specific to DSRCTs.4

DSRCTs typically arise from abdominal and pelvic peritoneum and spread over serosal surfaces, leaving multiple small peritoneal implants. There have been a small number of reports of DSRCTs affecting other organs, such as lymph nodes, ovaries, kidneys, pancreas, tunica vaginalis, testis, liver, and pleura. Such tumors arising within the cranium are extremely rare. Three definite and two possible cases of intracranial DSRCTs (one tentorial, one cerebellopontine angle, one temporal lobe, and two cerebellar tumors) have been previously reported.1,7,10,11 Here we report the first case of intracranial DSRCT presenting as
a suprasellar mass. The tumor caused panhypopituitarism and visual field defects as a result of optic chiasm compression in a young man and had a fatal outcome because of progressive disease.

Case Report

History and Examination

A 27-year-old man was referred to the endocrinology clinic with a history of excessive tiredness, lethargy, and loss of libido. He had a medical history of depression and had been treated with fluoxetine. His secondary sexual characteristics were normal, but he had a reduced testicular volume (12 ml) bilaterally. There were no clinical features to suggest the presence of acromegaly or Cushing’s disease. His visual fields were full to confrontation, and no neurological deficits were identified during clinical examination on his initial visit. Blood tests revealed panhypopituitarism with the following parameters: testosterone < 0.4 nmol/L (normal range 8.5–29 nmol/L), undetectable luteinizing hormone and follicle-stimulating hormone, random cortisol 14 nmol/L, thyroid-stimulating hormone < 0.01 mIU/L (normal range 0.4–4.5 mIU/L), free T4 9.3 pmol/L (normal range 10–23 pmol/L), insulin-like growth factor–I 11 nmol/L (age and sex-adjusted normal range < 0.4 nmol/L), prolactin 835 mIU/L (normal < 350 mIU/L). The patient’s endocrinology history was complicated by diabetes insipidus postsurgery and began treatment with desmopressin. His secondary sexual characteristics were normal, but he had a reduced testicular volume (12 ml) bilaterally. There were no clinical features to suggest the presence of acromegaly or Cushing’s disease. His visual fields were full to confrontation, and no neurological deficits were identified during clinical examination on his initial visit. Blood tests revealed panhypopituitarism with the following parameters: testosterone < 0.4 nmol/L (normal range 8.5–29 nmol/L), undetectable luteinizing hormone and follicle-stimulating hormone, random cortisol 14 nmol/L, thyroid-stimulating hormone < 0.01 mIU/L (normal range 0.4–4.5 mIU/L), free T4 9.3 pmol/L (normal range 10–23 pmol/L), insulin-like growth factor–I 11 nmol/L (age and sex-adjusted normal range < 0.4 nmol/L), prolactin 835 mIU/L (normal < 350 mIU/L). The patient’s treatment regimen began with replacement doses of hydrocortisone followed by levothyroxine. Gadolinium-enhanced MRI showed a large suprasellar heterogeneously enhancing mass extending into the third ventricle, compressing the optic chiasm, and downward to the pituitary fossa (Fig. 1A). No abnormality was detected in the rest of the brain. The patient was referred for urgent neurosurgical and ophthalmic assessments, but he failed to attend these appointments as well as further endocrine follow-up appointments.

Operation

A year later, the patient presented to the emergency department with worsening frontal headaches, drowsiness, and bitemporal hemianopia. Repeat MRI demonstrated a significant increase in the size of the suprasellar tumor (Fig. 1B). He was admitted to the neurosurgical unit, underwent a right frontoparietal craniotomy, and had near total removal of the tumor (Fig. 1C). He developed central diabetes insipidus postsurgery and began treatment with desmopressin while continuing with hydrocortisone and levothyroxine replacement therapy.

Pathology Findings

Histological examination revealed a tumor consisting of nests and cords of fairly uniform tumor cells characterized by hyperchromatic nuclei and indistinct cytoplasm distributed in a desmoplastic stroma (Fig. 2A). Some tumor cell nests appeared obliterated by dystrophic calcification. Mitotic activity and necrosis were discernible in the cell nests. Immunohistochemical staining revealed strong diffuse immunopositivity for cytokeratin CAM 5.2, vimentin, and desmin (Fig. 2B). Desmin (Fig. 2B) and placental alkaline phosphatase (PLAP) (Fig. 2C) staining demonstrated strong paranuclear dot to curvilinear positivity in a significant proportion of tumor cells. A subset of tumor cells that was dispersed through the nests also showed positivity for neurofilament protein and focal weak staining with neuron-specific enolase (Fig. 2D).

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Strong but patchy positivity was seen with epithelial membrane antigen (EMA), with focal positivity for CK7 and CK20. The tumor cells were negative for chromogranin, synaptophysin, CD56, CD99, SI00, and WT-1 (aminoterminal antibody used). Fluorescent in situ hybridization (FISH) analysis using the EWSR1 gene probe (Vysis LSI EWSR1 Dual Color Break Apart Probe, Abbott Molecular) demonstrated EWSR1 gene arrangement in multiple tissue areas. Reverse transcription polymerase chain reaction (RT-PCR) analysis with DNA sequencing of the PCR product confirmed an EWS exon 8/WT1 exon 8 translocation (Fig. 2D). Strong but patchy positivity was seen with epithelial membrane antigen (EMA), with focal positivity for CK7 and CK20. The tumor cells were negative for chromogranin, synaptophysin, CD56, CD99, SI00, and WT-1 (aminoterminal antibody used). Fluorescent in situ hybridization (FISH) analysis using the EWSR1 gene probe (Vysis LSI EWSR1 Dual Color Break Apart Probe, Abbott Molecular) demonstrated EWSR1 gene arrangement in multiple tissue areas. Reverse transcription polymerase chain reaction (RT-PCR) analysis with DNA sequencing of the PCR product confirmed an EWS exon 8/WT1 exon 8 translocation and EWS-WT1 transcript corroborating the diagnosis of DSRCT. Thus, the cytoarchitectural features, immunophenotype, and genotype were consistent with a diagnosis of DSRCT.

Radiology Findings

Immediate postoperative CT scans of the thorax, abdomen, and pelvis showed no evidence of a primary malignancy elsewhere, supporting that the DSRCT in the suprasellar region represented a primary CNS tumor and not a metastatic deposit. An MRI scan obtained 4 months after craniotomy revealed rapid expansion of the suprasell-
lar tumor remnant measuring 4.5 × 3.5 cm (Fig. 1D). The patient started receiving fractionated conformal radiotherapy, but treatment was discontinued after 1 week because of general deterioration in his condition. A repeat CT scan of the thorax, abdomen, and pelvis showed extensive metastatic disease involving mediastinal, subcarinal, and hilar lymph nodes, causing occlusion of the right main bronchus and right pulmonary infiltrates. No intraabdominal masses or lymph nodes were identified, and the appearances of the liver, spleen, and adrenal glands were normal. The histological results of a fine-needle aspirate obtained from a cervical lymph node were once again consistent with DSRCT. Palliative chemotherapy was considered; however, the patient’s clinical condition deteriorated rapidly and he died 20 months after his initial presentation.

Discussion

An intracranial DSRCT presenting as a suprasellar mass poses a major challenge in diagnosis and management. A tissue biopsy is essential to differentiate this lesion from other suprasellar tumors, such as invasive pituitary adenomas, craniopharyngiomas, gliomas, meningiomas, and metastases. Although the majority of DSRCTs have characteristic histological features, a significant proportion can exhibit a wide range of morphological features. The main differential diagnoses for these tumors presenting in the CNS based on histological findings should include medulloblastomas, atypical teratoid/rhabdoid tumors, and primitive neuroectodermal tumors. Immunocytochemistry and molecular genetics help to distinguish DSRCTs reliably from other tumors.

Cytogenetic analysis in DSRCTs has shown a specific chromosomal abnormality, t(11;22)(p13;q12), as a result of gene translocation and rearrangement of the genes for EWS and WT1. This can be demonstrated by RT-PCR or by FISH. The authors of a large series of DSRCTs reported a significant variation in clinical features, cytology, and immunoreactivity, but the gene fusion EWS-WT1 was consistently distinctive to this tumor. Histological examination, immunocytochemistry, and genotyping in our case demonstrated features typical of a DSRCT, which are quite distinct from the other tumors mentioned above.

The rare occurrence of these tumors makes the study of different treatment modalities and their impact on survival very difficult. Kushner et al. showed that intense alkylator-based therapy with the P6 protocol (cyclophosphamide, doxorubicin, vincristine, ifosfamide, and etoposide) improved remission rates in patients with intraabdominal or pelvic DSRCTs. In that study, 7 of 12 patients achieved a short-term remission, and 4 had complete remission for over 1 year. Quaglia and Brennan studied 40 patients, 27 of whom had intraabdominal tumors. Overall survival at 3 years from diagnosis was 29%, and induction chemotherapy with P6 protocol and gross-total resection of the tumor were associated with improved survival. Lal et al. showed that multimodality treatment improved the survival rate in a study of 66 patients with predominantly intraabdominal tumors. The 3-year survival rate was 55% in patients receiving induction chemotherapy (P6 protocol) combined with surgical debulking and radiotherapy.

Systematic review of the literature yielded only 5 cases of intracranial DSRCTs. Evaluation of presenting symptoms, pathological findings, management, and outcome of these limited cases shows the aggressive nature of these tumors despite multiple modalities of treatment (Table 1). Tison et al. reported on a 24-year-old man with posterior cranial fossa tumor adherent to the tentorium. This patient underwent a partial excision of the tumor and received 3 cycles of chemotherapy (PCNU cisplatin and V16) combined with radiotherapy and was receiving intracranial methotrexate at the time the study was published. There are no details published on long-term survival for this patient. Neder et al. reported on 2 cases of DSRCT. The first patient was a 37-year-old man with a cerebellar pontine angle tumor. He underwent subtotal resection and stereotactic irradiation but the disease progressed to spinal metastases 6 months later. He died 2 years after diagnosis despite receiving whole-brain and whole-spine radiotherapy and chemotherapy. The second patient was a 39-year-old man, with multiple lesions in the left cerebellar hemisphere and spinal leptomeninges, who presented with cauda equina syndrome. He underwent surgical decompression of the spinal cord and conus medullaris followed by radiotherapy and 3 courses of chemotherapy. He developed further posterior fossa and spinal axis lesions 27 months after diagnosis.

Yachnis et al. described a possible DSRCT in a 9-month-old girl with an aggressive posterior cranial fossa tumor requiring the placement of a ventriculoperitoneal shunt for obstructive hydrocephalus. She required a second craniotomy for tumor debulking surgery 18 months later despite intensive chemotherapy. Long-term survival details of this patient are not available. Bouchireb et al. described a 6-year-old girl with a right temporal lobe tumor in whom histological and immunohistochemistry findings

FIG. 2. A: Nests of tumor cells with hyperchromatic nuclei and indistinct cytoplasm surrounded by desmoplastic stroma. H & E stain, original magnification ×100. B: paranuclear dot and curvilinear desmin immunopositivity of tumor cells. Desmin, original magnification ×400. C: Distinctive paranuclear curvilinear and dot positivity for PLAP. Original magnification ×100. D: Subset of tumor cells showing neurofilament immunostaining. Original magnification ×200. Figure is available in color online only.
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<th>Authors &amp; Year</th>
<th>Age, Sex</th>
<th>Clinical Features on Initial Presentation</th>
<th>MRI Findings</th>
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<td>Yachnis et al., 1992</td>
<td>9 mos, F</td>
<td>Projectile vomiting &amp; increased head circumference</td>
<td>Enhancing rt cerebellar mass compressing &amp; displacing brainstem Marked obstructive hydrocephalus</td>
<td>Demarcated nests of tumor cells separated by mesenchymal stroma Nest cell positive for GFAP, cytokeratin, &amp; vimentin Negative for desmin immunoreactivity</td>
<td>None at time of publication</td>
<td>Ventriconstituental shunt Chemo w/ cisplatin, cyclophosphamide, vincristine, &amp; high-dose methotrexate Second craniotomy for debulking surgery 1.5 yrs after original presentation</td>
<td>Alive at time of publication</td>
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<tr>
<td>Tison et al., 1996</td>
<td>24 yrs, M</td>
<td>Headache, vomiting, vertigo, &amp; impaired hearing</td>
<td>Posterior cranial fossa tumor (3 × 4 × 3.5 cm) adherent to tentorium &amp; petrous part of temporal bone, displacing rt cerebellar hemisphere</td>
<td>Nests of small uniform round &amp; oval tumor cells separated by desmoplastic stroma Strong immunoreactivity for keratin, vimentin, desmin, &amp; EMA Southern blot for genomic DNA extraction, PCR analysis of EWS-WT1 fusion gene</td>
<td>None at time of publication</td>
<td>Partial excision of tumor Three cycles of chemo consisting of PCNU cisplatin &amp; V16; intracranial methotrexate every 40 days; radiotherapy</td>
<td>Alive &amp; no clinical signs of relapse at time of publication</td>
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<tr>
<td>Bouchireb et al., 2008</td>
<td>6 yrs, F</td>
<td>3-wk history of headaches, complex partial seizures, &amp; dysphasia</td>
<td>Well-demarcated heterogeneously enhancing mass in rt temporal lobe</td>
<td>Small malignant cells w/ hyperchromatic nuclei &amp; eosinophilic cytoplasm embedded in fibromyxoid stroma Positive staining for vimentin, desmin, &amp; synaptophysin EWS-WT1 translocation by FISH</td>
<td>None at time of publication</td>
<td>Complete excision of tumor Seven courses of chemo w/ P6 protocol (cyclophosphamide, doxorubicin, vincristine, ifosfamide, &amp; etoposide); focal conformal radiotherapy to tumor bed at 54 Gy</td>
<td>Alive &amp; disease free after 18 mos of follow-up</td>
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<td>Neder et al., 2009</td>
<td>37 yrs, M</td>
<td>5-mo history of lt side hearing loss &amp; tinnitus</td>
<td>Heterogeneously enhancing mass in lt CPA w/ mild mass effect</td>
<td>Intracranial &amp; spinal biopsies: round to oval hyperchromatic nuclei w/ inconspicuous nucleoli in addition to desmoplastic stroma Positive staining for EMA, CAM 5.2, desmin, &amp; nuclear INI-1 EWS-WT1 translocation by RT-PCR &amp; FISH</td>
<td>Spinal leptomeninges 6 mos after diagnosis</td>
<td>Initial subtotal resection of CPA mass &amp; stereotactic radiation to tumor bed Debulking of intradural spinal nodules &amp; spinal radiation (4500 rad); radiosurgery to CPA (100 rad) &amp; whole brain (3600 rad) Chemo (carboplatin temozolomide)</td>
<td>Died 2 yrs after diagnosis w/ progressive disease</td>
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<td>39 yrs, M</td>
<td>4-mo history of gait imbalance &amp; bilat lower limb weakness; later developed urinary &amp; fecal incontinence</td>
<td>Multiple enhancing lesions in lt cerebellar hemisphere &amp; metastasis in spinal leptomeningeal space</td>
<td>Laminectomy samples: tumor cells w/ oval to irregular nuclei w/ coarse chromatin &amp; scanty cytoplasm; positive staining for EMA, CAM 5.2, desmin, &amp; nuclear INI-1; EWS-WT1 translocation by RT-PCR</td>
<td>Metastasis to spinal leptomeningeal space at presentation</td>
<td>Decompression of spinal cord &amp; conus medullaris followed by radiotherapy Laminectomy of T12–L5 showed cauda equina nerve roots studded w/ gray tumor nodules Three courses of chemo (cisplatin, etoposide, &amp; Holoxan)</td>
<td>Increase in posterior fossa tumor; further spread in spinal axis after 27 mos of follow-up</td>
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Chemo = chemotherapy; CPA = cerebellopontine angle.
were not diagnostic of DSRCT but had the characteristic EWS-WT1 translocation. This patient underwent excision of the mass followed by P6 protocol chemotherapy and focal conformal irradiation of tumor bed at 54 Gy. She was reported to be free of the disease 18 months after diagnosis.

In summary, we have described the first case of an intracranial DSRCT presenting as a suprasellar mass, causing panhypopituitarism and bitemporal hemianopia in a young man who died of progressive disease. Despite multimodality treatment, the aggressive behavior of this tumor was similar to DSRCTs arising from the peritoneal cavity and the few rare intracranial cases. Failure to attend follow-up outpatient appointments and possible noncompliance with treatment may have also contributed to the poor prognosis in our patient. It is important to include DSRCTs in the differential diagnosis of an unusual suprasellar mass in young adults. Once the tumor is identified histologically, gross-total resection and radical postoperative treatment involving radiotherapy, chemotherapy, and close surveillance are required because of its potential for an aggressive clinical course.

References

Author Contributions
Conception and design: Thondam, Daousi. Acquisition of data: Thondam, du Plessis, Das, Haylock, Daousi. Drafting the article: Thondam, du Plessis, Cuthbertson, Daousi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Thondam.

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