CASE REPORT   **PEER REVIEWED | OPEN ACCESS**

Well controlled atypical central neurocytoma by CyberKnife radiosurgery: Review of the literature with a case report

Sema Yilmaz Rakici, Vaner Koksal, Recep Bedir, Eylem Odabasi

ABSTRACT

Introduction: Central neurocytomas are rare primary central nervous system tumors. The main treatment method is gross total surgical resection that can only be performed in half of the patients. As the possibility of relapse is higher, post-resection treatment of the remaining tumor is also important. Therefore, additional treatment is needed.

Case Report: We present a 29-year-old patient with atypical central neurocytomas whose residual tumors were well controlled by CyberKnife Robotic Surgery or Radiosurgery (CKRS).

Conclusion: In central neurocytomas, known to be excessively radiosensitive, stereotactic radiosurgery is a more preferred option due to its lower toxicity as an alternative treatment modality. CyberKnife robotic surgery, the latest radiosurgical method, has never been used in cases of central neurocytoma. The patient was well treated and the prognosis seems favorable so far.

Keywords: 1p19q Deletion, Central atypical neurocytoma, MIB-1 LI, Radiosurgery

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INTRODUCTION

Central neurocytoma (CN) was firstly described by Hassoun et al. in 1982 [1]. They comprise 0.1–0.5% of all primary brain tumors [2]. Due to the intraventricular localization of the tumors, the patients are usually admit to the hospital with hydrocephaly symptoms based on the obstructions in cerebrospinal fluid (CSF) flow. Computed tomography scan (CT) and magnetic resonance imaging (MRI) are beneficial for radiological diagnosis and locating the tumors. No firmly established diagnostic criteria exist to distinguish these tumors radiologically in CT scans and MRI from other tumors such as oligodendrogliomas. Because of some undetected features, biopsy or surgical resection when available is necessary to establish a final diagnosis [3]. Central neurocytoma is termed as a grade II benign brain tumor by World Health Organization (WHO). Since its first description, treatment modalities have changed. Although initially surgery was the only option, adjuvant or curative radiotherapy (RT) is currently available as a treatment option [4]. Although chemotherapy is not a primary treatment modality for CN, it has been used as an adjuvant or salvage therapy for recurrent CNs or inoperable patients [5].

The radiation history initially starting with the conventional external beam radiotherapy (EBRT) progressed parallel to the technological developments in RT with gamma knife radiosurgery (GKRS), linear accelerator stereotactic radiosurgery (LSRS), and proton

treatment applications. Recent studies have reported that stereotactic RT (SRT) is eligible for use in postoperative remnants and relapse [4, 6]. Schild et al. [7] have reported the first CN case incompletely resected and treated with GKRS in 1997.

Stereotactic radiosurgery (SRS) can be used as an alternative treatment option for CNs due to its ability to deliver high doses to target volume and rapid dose drop off in normal tissues. CyberKnife Robotic Surgery (CKRS) (Accuray, Sunnyvale, CA, USA) was developed in 1990s as a frameless image-guided SRS technique [8] and even though it has never been used for the patients with CN, it has been reported that it may be an alternative SRS technique due to its wide range of application in similar diseases [9]. In this study, we present a report of CKRS experience in CN which has not been previously reported in the literature.

CASE REPORT

A 29-year-old male admitted to the hospital due to the complaints of gait disturbance, weakness, and non-dermatomal pain in right leg. Initially he was diagnosed with lumbar disc herniation. Then the patient was hospitalized in department of neurosurgery and the presence of mild right hemiparesis. Brain MRI revealed a heterogeneous huge intraventricular and mild contrast tumor that partially invades nucleus caudatus and thalamus originating from the upper mesencephalon filling the third ventricle and the hydrocephalus as a consequence of this tumor. Absence of excess periventricular edema in T2 flair weighted images was a proof of slowly progressive hydrocephalus. The gait disorder was related to this situation but the patient had no obvious complaints of headache. The patient's hydrocephalus had not yet caused an increase in intracranial pressure significantly (Figures 1(A–C, E)–3).

Surgical therapy

The patient's head was fixed with pin frame in supine position. In order to reach the left lateral ventricle which was dominantly occupied by the tumor, anterior interhemispheric transcallosal approach was used and the dilated left lateral ventricle was entered in from the left parietal cortex (Figures 1D and 3). Using microsurgical techniques, tumor tissue inside the lateral ventricle was debulked in small pieces. Tumor was bleeding a lot due to its vascular structure. A part of tumors the lateral ventricle was removed easily because of its cleavage from the walls. Foramen of Monro was not seen. A harder tumor was encountered as it progressed to the base of the tumor during surgery. Postoperative follow-up CT revealed that this unresectable part was the solid calcified part of the tumor. As the patient's CSF flow was not fully re-established and the remnant mass could increase the hydrocephalus, ventriculoperitoneal (VP) shunt was placed in the same session following the subtotal mass resection to avoid permanent neurologic deficit. The patient was discharged with a slight right-sided hemiparesis in postoperative early period but he was fully recovered after ten days.

Pathology

In the microscopic examination tumor was composed of a uniform population of round cells with scant cytoplasm in a fibrillary background (Figure 4A). Common calcification was observed in tumor cells (Figure 4B). In the immunohistochemical examination, NSE diffuse (+), synaptophysin diffuse (+), chromogranin (−), MAP2 (+), neurofilament protein (NFP) (−), IDH-1 (−), epithelial membrane antigen (EMA) (−), glial fibrillary acidic protein (GFAP), and Olig-2 showed focal (+) staining in the ground glial cells (Figure 4C and D). The mitotic activity (up to 4 mitoses/10 high power field) and the high percentage of MIB-1-staining in tumor cells (MIB-1 labeling index: MIB-1 LI) 4–5% (Figure 4E). Genetic examination for the differential diagnosis of intraventricular oligodendroglioma did not reveal 1p19q deletion. With finding was diagnosed atypical central neurocytoma.

Post-operative findings on MRI and CT

There was a dense mass lesion of about 43–25 mm in size, compressing the parenchyma of the brain, showing approximately 1 cm of shunt to the right of the midline filling the foramen of Monro level in the left lateral ventricle, containing calcifications in the nucleus caudatus and internal capsule around the left lateral ventricle (Figure 3). When compared with the preoperative mass volume, the mass of the tumor was found to be decreased by 50% and it still had a remnant inside.

Adjuvant RT

Due to the presence of the postoperative residual tumor, RT was decided. Single fraction CKRS was applied using the CKRS method to cover the 73% isodose curve. Radiation (14 Gy) was delivered to a prescription isodose line of 73% (Figure 5).

Brain MRI after CKRS

When the lesion is compared to the previous MR images, a remarkable decrease in size can be seen after injection of intravenous contrast (Figure 2). On the 12th months, especially T1 axial and T2 sagittal control MR sections revealed decreased tumor mass and increased edema in the brain parenchyma around the tumor. Edema was thought to be secondary to radiotherapy. However, no clinical effect was observed in the patient (Figure 2, column 4).
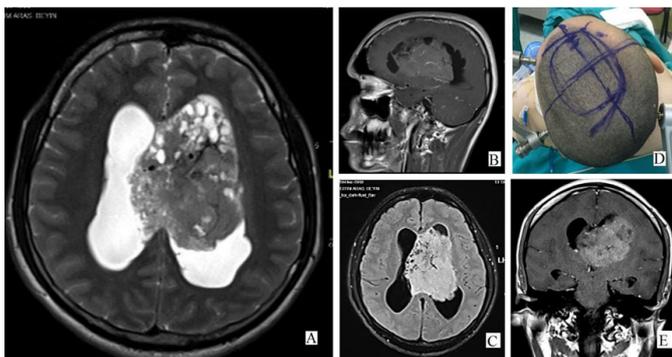
Figure 1: Radiological images in first diagnosis. (A, B, C, E) MRI of the brain: Hydrocephalic dilatation in both lateral and third ventricles is observed. Mass lesion of 60 × 57 × 51 mm with mid-level heterogeneous contrast enhancement in isointense post-contrast series of T1 and T2A-weighted images. Located in mid-intraventricular area extending to third and left lateral ventricles, attached to the base of the third ventricle and nucleus caudatus at the top, cystic areas, and vascular structures are seen. (D) Surgical position with Mayfield.

Figure 2: Follow-up magnetic resonance images of the patient. (column 1) Preoperative MR images. (column 2) Postoperative MR images. (column 3) MR images after CKRS at three months: The shrinkage of the mass is observed. (column 4) MRI after CKRS at 12 months. The shrinkage observed in the first three months was not detected in the MR imaging in the twelfth month (column 4). The residual mass was considered to have shrunk at the end of 12 months.
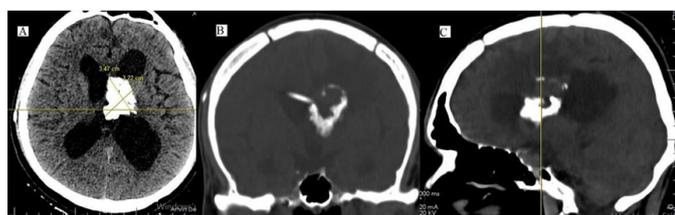
Figure 3: Latest computed tomography images of the patient. A mass located in left lateral ventricle with dense central solid calcifications, causing obstruction in CSF flow pathway is observed. It is understood that this condition belongs to the residual mass remaining after surgical resection. The CT section shows a calcified mass on the nucleus caudatus and thalamus. No tumor in the third ventricle.
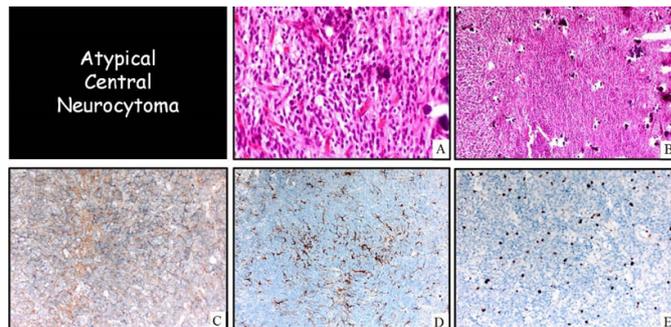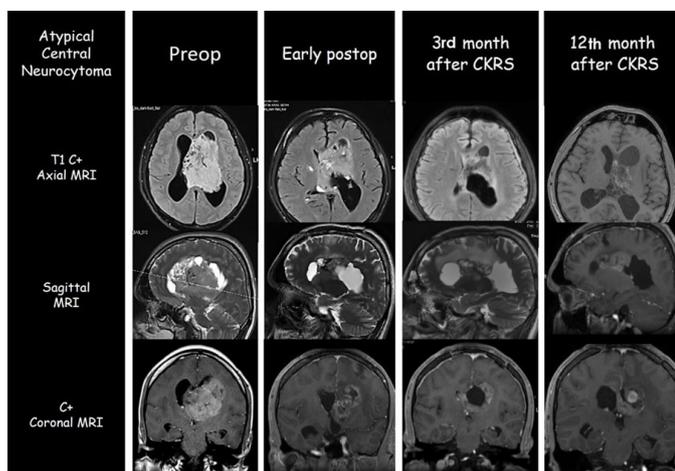

Figure 4: Pathological images. (A) The tumor was composed of a uniform population of round cells with scant cytoplasm in a fibrillary background (H&E ×400). (B) Common calcification was observed in tumor cells (H&E ×100). (C) Synaptophysin positive staining was observed in tumor cells (×200). (D) GFAP positive was observed in glial cells of the tumor (×200). (E) A low proliferative index of MIB-1 LI in tumor was observed (×200).
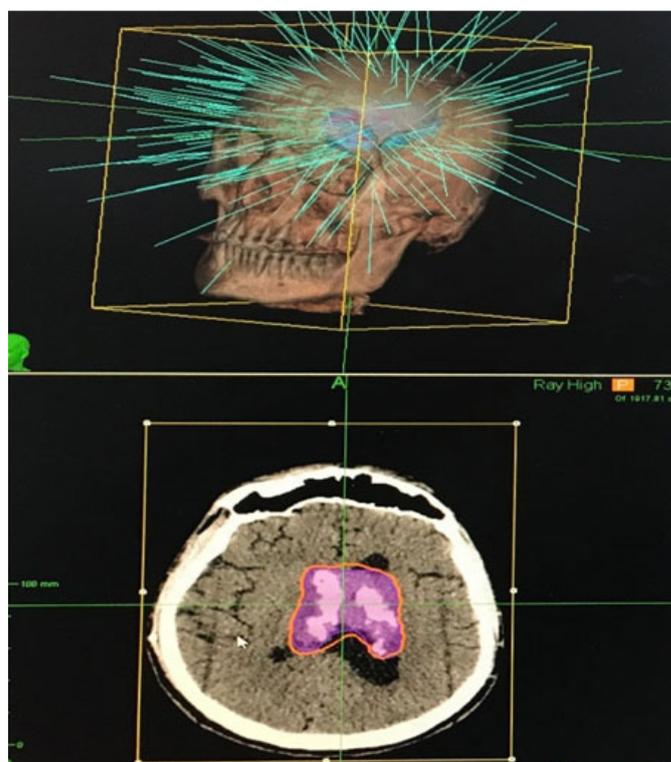

Figure 5: Radiotherapy images. Above, the patient and beam's eye view (BEV) projection and digitally reconstructed radiography images are shown, below, the isodose curve surrounding target volume in axial CT section is shown.

DISCUSSION

Central neurocytoma is usually diagnosed between 20 and 40 years of age and typically affects young adults around the third decade [2, 3]. Although most studies in the literature suggest that the disease is more frequently seen in males [10], it is reported that both sexes are equally affected [11]. Symptoms in CN

cases usually occur as a result of the mass effect of the tumor or due to the impact of the site [1]. In addition, due to obstructive hydrocephalus caused by impaired cerebrospinal fluid flow, increased intracranial pressure, epileptic seizure, headache, nausea, vomiting, memory, and visual disturbances may occur [2, 5]. Our patient had mild paresis-related gait disturbance in the right lower extremity and mild headache due to hydrocephalus. As pain in the soles of the feet were included in the clinical complaints, initially focused on lumbar disc herniation. Similar cases are reported in the literature and in the presence of parasagittal tumors on cerebral hemispheres, drop foot clinic only may inadvertently cause lumbar spinal interventions as a result of inadequate clinical and radiological evaluation [12, 13].

Cranial CT images in CN cases typically originate around the foramen of Monro. In most cases, CT images show areas of calcification and hypodense cystic degeneration [2, 11]. On cranial MR imaging, the mass usually appears as isointense on T1-weighted images and in majority of the cases, on T2-weighted images the mass is relatively isoindense with the cortex and there is usually a moderate increase after gadolinium administration [14, 15]. In the pathological examination of CN, the rate of proliferation is low. In some cases, anaplastic features such as microvascular proliferation, necrosis, and increased mitotic activity (MIB-1 LI> 2%) may be seen. In these tumors, the recurrence rate is higher than the classical type neurocytomas and the survival rate is lower. MIB-1 LI> 2% is an important prognostic factor for local control and overall survival in central neurocytoma [16]. It was reported that recurrence rate and craniospinal spread were significantly higher in cases with MIB-1 LI> 2% [17, 18]. Atypical neurocytoma was first described in the literature in 1997 by Söylemezoglu et al. as a new entity [17]. In this study (36 patients), the histological features and proliferation potential were compared with clinical results. The relapse rates in the 150-month follow-up were 63% in MIB-1 LI> 2%, and 22% in those below 2%. For this reason, tumors which were MIB-1 LI> 2% were recommended to be called as atypical neurocytoma [17]. Mackenzie et al. have identified that all cases with symptomatic tumor recurrence had MIB-1 LI above 2%, and they stated that it would be a more appropriate approach to call these tumors as the proliferating neurocytomas rather than the atypical or anaplastic neurocytoma [18]. We can easily suggest that, in cases of MIB-1 LI> 2%, vascular proliferation and necrosis, or both, CN cases are defined as atypical neurocytoma. In our case, the results on the mitotic activity (up to 4 mitoses/10 high power field) and the high percentage of MIB-1-staining in tumor cells which MIB-1 LI was 4–5% were found to be consistent with the atypical central neurocytoma.

Surgical removal of these tumors is the preferred treatment modality. In addition, adjuvant RT is increasingly being used. Many studies suggest that both conventional RT and SRS are useful in residual tumor cases after subtotal resection and in tumor recurrence [6, 19]. In cases which gross total resection (GTR) is eligible to perform, surgical treatment with a 5-year survival rate of 99% can be considered curative [6]. However, due to the location of the tumor, GTR can be performed only in 30–50% of all cases [20]. Therefore, adjuvant therapy is frequently required after subtotal resection (STR) [20, 21]. Moreover, the CNs are radiosensitive [22]. This situation leads to the recommendation of postoperative RT as an effective treatment for patients with residual tumors.

The role of RT as an adjuvant treatment in patients who have had GTR and without atypical pathology is controversial due to the already good local control rates [23, 24]. Because after RT applications, side effects associated with long-term cognitive function may occur [25, 26]. After 10 years of follow-up after conventional RT, side effects which may impair quality of life in long-term follow-up have been reported [25, 26]. In contrast, it is possible to prevent the severe parenchymal damage caused by conventional RT by the help of advanced RT techniques, such as fractionated SRT, 3D conformal RT, or SRS. As known, SRS has been used as an alternative treatment option for CNs due to the rapid dose fall-off. Rades et al. [24] have compared the results of the patients who underwent postoperative SRS and conventional RT and emphasized that the results of both radiation treatments were similar, and that SRS was a reasonable alternative therapy that provided tumor control with similar survival rate without the side effects of conventional RT. With RS, a high dose of radiation can usually be given to a small volume with a single fraction, creating minimal damage to the surrounding normal brain parenchyma [20]. In this way, while high doses can be given to specified target volume, a fast dose drop-off occurs in normal tissues other than the target volume. Central neurocytoma appears to be a good candidate for CKRS when evaluated together with its intraventricular location and radiosensitive characteristics. Stereotactic radiosurgery applications can be performed by techniques such as LSRS, GKRS, and CKRS which is called the robotic radiosurgery. Although limited to a small number of reports, the results of LSRS application in CN have been positive [22]. Kim et al. [27] have used LSRS in post-surgical management of recurrent lesion. According to the results of this study, it was determined that the tumor started to shrink within six months after SRS and completely disappeared after 36 months. In 1997, Schild et al. [7] have reported the first case of an incompletely resected CN treated by GKRS. In later studies, it is seen that GKRS is used in CN [19]. In the 1990s, John Adler and the physicist Richard Cox developed a robotic radiosurgical system at Stanford University Medical Center and this system was commercialized as CyberKnife Accuray, Sunnyvale, CA [8]. In 1997, physicist Martin Murphy and his physician colleagues introduced CyberKnife robotic arm accelerator to Image-guided radiation therapy (IGRT) using a room-mounted kV

imaging system [8]. Although CyberKnife was originally designed for the treatment of intracranial lesions, it has been developed by CyberKnife users to be easily applied for targets in the spine and other extracranial regions.

There is no sufficient information about the use of CyberKnife for CN in literature. However, it can be used in CN cases due to its application in similar diseases and it can be used as an alternative RT technique [9]. We believe that this case will be useful in providing evidence for use of CyberKnife in CN and showing treatment results. It is suggested that the optimal dose for local control in the conventional fractionation of CN is a total of 54 Gy or more in a daily dose of 2 Gy fractions [28]. It is also stated that the negative effects due to the radiation toxicity limiting the dose will be minimal if it does not exceed 60 Gy [22]. Thus, for patients with CN, the optimal dose of RT in the conventional fraction appears to be in the range of 54–60 Gy in a daily dose of 2 Gy fractions [29]. Additional studies are needed to determine the optimal dose of SRS in CN. In a study recruiting 64 patients by Park and Steven [4] 58 (90.6%) cases of CN were treated with GKRS and 6 (9.4%) with LSRS. While surgical resection was performed in 56 cases (87.5%) prior to SRS, SRS was used as the primary treatment in 8 (12.5%) cases. In cases with SRS as the primary treatment, CN diagnosis was confirmed with biopsies only in 2 of the patients and with MRI findings in 6 patients. In this study, it was observed that the radiation dose was given in one one session between 9 and 24 Gy depending on several factors (tumor volume, previous treatment, and tolerance of other structures) and no multi-session radiosurgery was performed. The cause of nine local failures has been suggested as the insufficient dose in patients who underwent SRS. In conclusion, the mean marginal dose for local recurrence was found to be 12.8 Gy when compared with patients who received 15.6 Gy. Also, the mean dose and local control were significantly correlated in this study. In addition, despite the small sample size, it was also emphasized that radiation dose may contribute to local control in this study. Matsunaga et al. [19] reported that local control improved with marginal doses in the range of 13–18 Gy. Therefore, a marginal dose of at least 13 Gy was suggested for effective tumor control. In a meta-analysis with more patients (150 patients), 146 patients (97%) with CN were treated with GKRS and 4 patients (3%) with LSRS [6]. In this study, 125 patients (83.3%) underwent subtotal or total resection, while 25 patients (16.7%) underwent SRS as a primary treatment without any surgery. The average marginal dose of patients in this study was calculated as 14.7 Gy (dose range: 9–25 Gy).

We performed the first CKRS application in CN with a dose of 14 Gy in a single fraction, considering the tumor volume of our patient in accordance with the SRS doses in the literature, which is above 13 Gy. We determined that the tumor regressed in the first, third, and sixth month follow-up radiological imaging after SRS. Because of the benign nature of these tumors, although most patients tend to present a positive outcome after treatment,

recurrence rates seem to be relatively high. In Schild et al.'s study [7], patients with GTR and without adjuvant RT, local control and 5-year survival rates were 100% and 90%, respectively. However, in STR patients these rates were determined as 70% and 77%, respectively. In this study, it was reported that local control rate increased from 50% to 100% by the administration of adjuvant RT in patients with STR. The 5-year overall survival rate was 88% in patients who underwent RT and 71% in those who did not receive RT. Radiotherapy after GTR does not increase local control or 5-year survival rate. In Rades et al.'s study [30], (a total of 85 patients) 3-year and 5-year local control rates were as follows: 73% and 57% for GTR and 21% and 7% for STR. 3-year and 5-year survival rates were: 93% and 93% after GTR and 65% and 43% after STR, respectively. With the addition of adjuvant RT, 3-year and 5-year local control rates for GTR cases were 81% and 53%, respectively, and increased to 85% and 70% in STR cases, respectively. Similarly, 3-year and 5-year survival rates for those with adjuvant RT remained at 90% and 90%, respectively, while these rates increased to 87% and 78%, respectively, STR cases. As seen, in patients with atypical CN, post-STR administration of RT significantly increased local control and survival rates, whereas GTR-treated cases did not show similar positive results with RT after SRS, treatment-related complications such as hemorrhage including intracerebral and tumoral, cerebral edema, and radiation damage can be seen [6]. In our patient, a small area of hemorrhage was detected at MRI on third month. Hemorrhage without clinical effects was lost in subsequent radiological follow-up.

CONCLUSION

Stereotactic radiosurgery (SRS) is a good alternative to conventional RT, it allows the patient to be treated in a single session thus avoiding the need for surgery again. Atypical central neurocytoma has shrunk significantly after the SRS in the early twelve months period.

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Author Contributions

Sema Yilmaz Rakici – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Vaner Koksal – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Eylem Odabasi – Conception of the work, Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

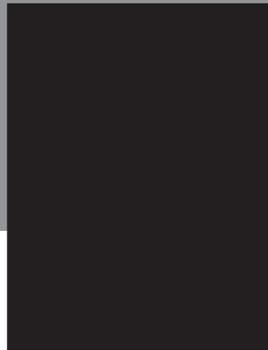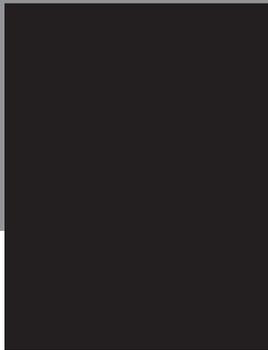All relevant data are within the paper and its Supporting Information files.

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