Background. Patients presenting with synchronous bifocal intracranial tumors (masses in the pineal and neurohypophyseal region), detectable human chorionic gonadotropin (hCG) levels (5–100 mIU/mL), and normal alpha fetoprotein (AFP) levels (<10 ng/mL) are often diagnosed empirically with pure germinoma. In such scenarios, pathologic confirmation is often deferred, given that bifocal nongerminomatous germ cell tumors (NGGCTs) are considered rare and because available literature and research protocols support such an approach. We sought to characterize the association between bifocal intracranial tumors and NGGCT histology.

Methods. Seventy-one patients treated for intracranial germ cell tumors at Massachusetts General Hospital in 1998–2012 were identified. Patients presenting with synchronous bifocal disease were selected for further review.

Results. Of the 71 patients presenting with intracranial germ cell tumors, 14 (19.7%) had synchronous bifocal disease. Of these 14 patients, 7 (50.0%) had germinoma, 3 (21.4%) had NGGCT, and 4 (28.6%) had hCG levels, 200 mIU/mL and normal AFP levels and were treated without pathologic confirmation. Of the 3 patients with confirmed bifocal NGGCT, 2 had detectable hCG levels with AFP <10 ng/mL and 1 patient had a detectable hCG level with a modest elevation in AFP.

Conclusions. NGGCTs should be considered in the differential diagnosis for patients presenting with bifocal intracranial tumors. Given differences in the management of germinomas and NGGCTs, clinicians should strongly consider a biopsy in patients presenting with bifocal masses and normal or modestly elevated biomarkers. Misclassification of such cases as germinomas could result in undertreatment and a possible increased risk for recurrence.

Keywords: bifocal, germ cell, multiple midline, NGGCT, nongerminomatous.
levels (≤10 ng/mL) is pathognomonic for germinoma,2,4–6 as reports of presentation of NGGCTs in a similar manner are virtually nonexistent.7,8 As a result, some authors have asserted that cases presenting with synchronous bifocal masses, detectable hCG levels, and normal AFP do not require pathologic confirmation and can be treated empirically as germinomas.3,5 The same approach is endorsed in the Children’s Oncology Group’s most recent protocol for intracranial GCT.10

The distinction between germinomas and NGGCTs is clinically important, as the radiation fields, radiation doses, role of surgery, and chemotherapy regimens employed in the management of germinomas and of NGGCTs differ significantly. Apart from mature teratomas, which are treated surgically and do not require chemotherapy or radiation, NGGCTs require more aggressive treatment approaches in order to achieve durable control, and improper classification of an NGGCT as a germinoma could result in undertreatment. Given that omission of biopsy in patients with bifocal intracranial tumors is supported by both existing literature3,9 and current protocols,10 reports of patients presenting with bifocal NGGCTs have clinical relevance. In this report, we describe 3 patients with bifocal NGGCTs who presented with detectable hCG levels and normal or modestly elevated AFP (n = 2 with AFP <10 ng/mL; n = 1 with AFP = 28 ng/mL), representing the only series of patients with bifocal NGGCTs ever published.

Methods

Seventy-one patients treated for intracranial GCTs at Massachusetts General Hospital between 1998 and 2012 were identified. As part of the staging workup, patients underwent an MRI of the brain and spine in addition to cytologic examination of the cerebrospinal fluid (CSF). Nearly all patients underwent hCG and AFP assays, both in the serum and in the CSF. Most patients with detectable hCG and normal AFP levels underwent pathologic confirmation of their disease. In the setting of significant elevation of AFP or hCG, the diagnosis of NGGCT was presumed and tissue confirmation was not obtained.

Of the 71 patients initially identified, 47 (66.2%) had germinomas, while 24 (33.8%) had NGGCTs or mixed tumors that harbored an NGGCT component. Patients who were found to have mixed tumors (germinoma + NGGCT other than mature teratoma) were treated as having NGGCTs given the established practice of classification based on the most malignant component of a tumor that is present.4 This study was approved by the institutional review board at our institution. Informed consent was waived for this retrospective study of existing patient records.

Results

Of the 71 patients in the study, 14 (19.7%) had synchronous bifocal disease at presentation. Of those with bifocal disease, 6 patients (42.9%) had pathologically proven germinoma (of these, 2 patients had a biopsy of the neurohypophyseal region and 4 had a biopsy of the pineal region; no patients underwent a biopsy of both regions), 3 patients (21.4%) had pathologically proven NGGCT (to be discussed in more detail), and 3 patients (21.4%) never underwent a biopsy (1 patient had a CSF hCG of 150 mIU/mL and received treatment for an NGGCT; the remainder were considered to have pure germinomas). In addition, 2 patients (14.3%) had neurohypophyseal masses, detectable hCG, non-elevated AFP, and modestly enlarged pineal glands that decreased in size with chemotherapy (one underwent biopsy of the neurohypophyseal region and was proven to have a germinoma, the other was treated without pathology as having a germinoma). Therefore, of the 14 patients with bifocal tumors, 7 (50.0%) had germinoma, 3 (21.4%) had NGGCT, 3 (21.4%) were treated as having germinoma without pathologic confirmation (which was not obtained due to patient refusal in 1 case and the perceived high-risk nature of the biopsy in 2 cases), and 1 (7.1%) patient was empirically treated for an NGGCT due to a CSF hCG of 150 mIU/mL. Of the 14 patients presenting with synchronous bifocal disease, 3 had confirmed NGGCTs and are further described here (and in Table 1).Of note, all patients with pathologically proven bifocal NGGCTs had their pathology assessed by an independent academic pathologist not affiliated with Massachusetts General Hospital, with perfect concordance between the reviews in all cases.

Patient 1 was 17 years of age when he developed headaches. An MRI of the brain revealed a 1.5 × 2.4-cm neurohypophyseal mass and a 3.3 × 3.4-cm pineal mass (Fig. 1). Gross total resection of the pineal tumor revealed a mixed GCT that contained a yolk sac component (the predominant histology within the tumor), germinoma, as well as mature teratomatous elements. A spine MRI and lumbar puncture were negative for metastatic disease. Serum and CSF hCG were 11 and 49 mIU/mL, respectively, and serum and CSF AFP levels were 5.6 and 3.0 ng/mL, respectively (institutional normal range for serum AFP: 0–7.5 ng/mL; the normal range for CSF AFP was not available). He received 6 cycles of chemotherapy (cyclophosphamide/etoposide alternating with ifosfamide/etoposide). The neurohypophyseal mass increased in size thereafter and was eventually resected, with pathology revealing mature teratoma with abundant fibrosis and necrosis. He received craniospinal irradiation (CSI) with protons to 36 cobalt gray equivalents (CGE) in 20 fractions, followed by an involved-field boost to the neurohypophyseal and pineal regions of 18 CGE in 10 fractions. He has not experienced a recurrence of his disease 3.5 years after completing therapy.

Patient 2 was 14 years old when he developed polyuria. He later developed headaches, emesis, and Parinaud’s syndrome. An MRI of the brain revealed a 2.5 × 2.2-cm pineal mass and a 0.4 × 0.6-cm mass along the pituitary stalk. An MRI of the spine and a lumbar puncture were negative for metastatic disease. Serum and CSF hCG were 5.3 and 28.7 mIU/mL, respectively, and serum and CSF AFP were 7.4 and 1.66 ng/mL (institutional
The pineal tumor was biopsied and revealed a mixed yolk sac tumor and germinoma (Fig. 2). He received 6 cycles of chemotherapy (carboplatin/etoposide alternating with ifosfamide/etoposide). The pineal tumor decreased in size and the neurohypophyseal lesion resolved completely. He received CSI with protons to 27 CGE in 18 fractions followed by an involved-field boost to the neurohypophyseal and pineal regions of 27 CGE in 18 fractions. He has not experienced a recurrence of his disease 2.0 years after completing therapy.

Patient 3 was 17 years old when he developed polyuria, drowsiness, and Parinaud’s syndrome. An MRI of the brain revealed a 1.9 × 1.3-cm pineal tumor. Although no abnormal masses were seen in the neurohypophyseal region, the presence of multiple endocrinopathies at diagnosis was thought to be indicative of occult disease. Serum and CSF hCG were 4.7 and 7.6 mIU/mL, respectively; serum and CSF AFP were 28 and 2.0 ng/mL (institutional normal range for serum AFP: 0–7.5 ng/mL; the normal range for CSF AFP was not available). An MRI of the spine was unremarkable. A biopsy of the pineal tumor revealed a yolk sac tumor. He received 6 cycles of chemotherapy (carboplatin/etoposide alternating with ifosfamide/etoposide) and his pineal tumor resolved completely. He received CSI with protons to 36 CGE in 36, 54 NED.

**Table 1.** Characteristics of patients presenting with bifocal NGGCTs

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age at Dx (y)</th>
<th>Year of Dx</th>
<th>Pretherapy Histology (N:P)</th>
<th>Pretherapy s-hCG (mIU/mL)</th>
<th>Pretherapy s-AFP (ng/mL)</th>
<th>Pretherapy CSF hCG (mIU/mL)</th>
<th>Pretherapy CSF AFP (ng/mL)</th>
<th>RT Volume</th>
<th>RT Dose (CSI, total)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>17</td>
<td>2008</td>
<td>Unknown; Y/T/G&lt;sup&gt;a&lt;/sup&gt;</td>
<td>WNL</td>
<td>&lt;10</td>
<td>WNL</td>
<td>&lt;10</td>
<td>CSI, IF boost</td>
<td>36, 54</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>14</td>
<td>2010</td>
<td>Unknown; Y/G</td>
<td>WNL</td>
<td>&lt;10</td>
<td>WNL</td>
<td>&lt;10</td>
<td>CSI, IF boost</td>
<td>27, 54</td>
<td>NED</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>M</td>
<td>17</td>
<td>2008</td>
<td>Unknown; Y</td>
<td>WNL</td>
<td>28</td>
<td>WNL</td>
<td>&lt;10</td>
<td>CSI, IF boost</td>
<td>36, 50.4(S)/54(P)</td>
<td>NED</td>
</tr>
</tbody>
</table>

Abbreviations: Pt, patient; Dx, diagnosis; N, neurohypophyseal; P, pineal; s, serum; S, Suprasellar; RT, radiotherapy; CSI, craniospinal; Y, yolk sac tumor; T, teratoma (mature); G, germinoma; WNL, within normal limits for NGGCT (<50 mIU/mL); IF, involved field; NED, no evidence of disease.

<sup>a</sup>Yolk sac represented the dominant portion of the tumor.

<sup>b</sup>This patient had a pineal mass on imaging. However, diabetes insipidus and other endocrinopathies were present at diagnosis, indicating neurohypophyseal involvement.

**Fig. 1.** MRI at diagnosis for a patient with a bifocal, mixed NGGCT and germinoma. Displayed are sagittal (1a) T1 postcontrast and (1b) T2 weighted sequences, axial T1 postcontrast images of the (1c) pineal and (1d) neurohypophyseal regions, and coronal T1 postcontrast images of the (1e) pineal and (1f) neurohypophyseal regions. White arrowheads denote the neurohypophyseal mass; black arrowheads denote the pineal mass.
20 fractions followed by an involved-field boost to the neurohypophyseal and pineal regions of 14.4 CGE in 8 fractions and 18 CGE in 10 fractions, respectively. He has no evidence of recurrent disease 3.2 years after completion of treatment.

Discussion

To our knowledge, this is the first study to report that a relatively high proportion of patients with synchronous bifocal NGGCTs can present in the setting of detectable hCG levels and normal or modestly elevated levels of AFP. A very limited number of preceding studies have reported on bifocal presentation of NGGCTs, and most have presented only single cases.7,8,11 In a review of all GCT cases reported in the literature between 1950 and 1981, Jennings et al4 identified only 6 cases of bifocal NGGCT during this 31-year period; their study predated the routine use of biomarkers. Interestingly, isolated patients in published series of NGGCTs (not limited to bifocal presentation) have been shown to possess normal hCG and AFP levels, albeit rarely.12–14 It is important to note, however, that hCG and AFP levels are subject to variation and sampling error.

In our study, 21.4% of patients with bifocal GCT had an NGGCT, a detectable hCG level, and a normal or modestly elevated level of AFP. Our findings directly contradict elements of the existing literature and certain currently active research protocols, which stipulate that presentation with bifocal tumors is pathognomonic for germinoma and that such cases do not require pathologic confirmation.3,9,10 Of note, several prior protocols of the Children’s Oncology Group have required biopsy in such patients.15 Notably, biopsy of GCT patients without clear marker elevation is recommended outside of the setting of bifocal disease. However, given that many physicians assume that patients have germinomas when synchronous bifocal lesions are seen in the setting of detectable hCG but normal or modestly elevated AFP, the clinical impact of our findings is considerable, as our data indicate that a substantial percentage of such patients may have NGGCTs.

The importance of distinguishing germinomas from NGGCTs relates to the significant differences in clinical management of these respective tumors (see Table 2). Germinomas can be successfully treated with radiation alone, while NGGCTs require chemotherapy in addition to radiation, as outcomes in NGGCT patients given radiotherapy alone are dismal (survival ≈ 20%–45% at 5 y).4,16–18 However, with the addition of chemotherapy to surgery and CSI in the most recent Children’s Oncology Group study, patients with NGGCTs achieved a 2-year event-free survival rate of 84%.19 In addition to the difference in outcome for NGGCT patients receiving and not receiving chemotherapy, it is important to note that chemotherapy regimens for NGGCTs tend to be more aggressive and of longer duration than regimens used to treat germinomas.10,15

Radiotherapeutic management of germinomas and NGGCTs also differs. In the United States, radiation for nonmetastatic germinoma does not involve CSI given the minimal benefit and added toxicity of CSI in such patients,20,21 while radiation for localized NGGCT includes CSI, although omission of CSI is currently being investigated in the setting of the current Children’s Oncology Group clinical trial, ACNS1123.10 Doses of radiation also differ. When chemotherapy is employed for

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Table 2. Current approach to nonmetastatic germinoma and NGGCT in the United States

<table>
<thead>
<tr>
<th>Management Modality</th>
<th>Germinoma</th>
<th>NGGCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>C,E × 4 cycles</td>
<td>C,E alternating with I,E × 6 cycles</td>
</tr>
<tr>
<td>Radiation volume</td>
<td>WV + IF boost</td>
<td>CSI + IF boost (or WV + IF boost on protocol)</td>
</tr>
<tr>
<td>Radiation dose (total)</td>
<td>30–36 Gy</td>
<td>54 Gy</td>
</tr>
<tr>
<td>Need for neurosurgical resection</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Abbreviations: C, carboplatin; E, etoposide; WV, whole ventricle; IF, involved field; CSI, craniospinal irradiation; I, ifosfamide.
germinomas, radiation dose is reduced to 21 Gy for whole ventricle radiation (or 18 Gy on protocol) followed by involved-field boost to a total dose of 30–36 Gy, while in the United States NGGCTs are typically treated with CSI to 36 Gy (or whole ventricle radiation to 30.6 Gy, on trial10) followed by involved-field boost to a total dose of 34 Gy. Recurrence rates for NGGCTs appear to be greater if the total dose to the involved field is <50 Gy.22 Additionally, while surgery primarily has a diagnostic role in the management of germinomas given their marked chemo- and radiosensitivity, a substantial portion of patients with NGGCTs will require aggressive neurosurgical resection because of a more limited response to higher-intensity chemotherapy and radiation.23 Given the sharp divergence in the management of germinoma and NGGCT, establishing the correct diagnosis is crucial. For this reason, our report indicates that physicians should include NGGCT on the differential diagnosis when evaluating patients with bifocal disease and that consideration should be given to obtaining a biopsy, repeating tumor markers, and doing everything that can be safely achieved to ensure the proper diagnosis in the setting of bifocal disease and normal or modestly elevated biomarkers.

Whether patients presenting with bifocal lesions should undergo a biopsy of both the neurohypophyseal and pineal regions is not clear. Such an approach would reduce sampling error and provide histological assessment of both tumors, lowering the risk of undertreatment if one lesion harbored an NGGCT but the other contained only germinoma. However, given that obtaining tissue from both the pineal and neurohypophyseal regions during a single procedure is difficult, it is likely that separate procedures would be required. Novel approaches and continually improving technology have decreased the morbidity and mortality associated with intracranial biopsy, even when relatively deep structures such as the pineal region are targeted.24,25 O’Brien et al26 reviewed the outcomes of 41 patients who underwent single-trajectory endoscopic third ventriculostomy and endoscopic biopsy of a midline tumor. The procedure entailed introduction of a flexible endoscope into the lateral ventricle followed by passage through the foramen of Monro and entry into the third ventricle. Flexible biopsy forceps were introduced and a sample from the tumor was taken. The most common complications of surgery were sixth nerve palsy and hemorrhage, both of which were transient and associated with no long-term morbidity. No deaths were reported.26 Similar results have been reported for patients biopsied by stereotactic techniques, which are generally well tolerated but often necessitate a separate procedure for CSF diversion in patients who require it.26–28 Tissue samples obtained by stereotactic biopsy may also be smaller and are less likely to be representative of the histological components of the tumor, thus increasing the likelihood of sampling error and inappropriate treatment recommendations.28,29 Sampling of lesions in the neurohypophysis can often be accomplished in a minimally invasive manner through a transsphenoidal approach. Such an approach offers low morbidity and mortality, although CSF leakage, endocrine abnormalities involving the anterior pituitary, and diabetes insipidus may occur.30 In summary, given that sampling of tissue from both the pineal and neurohypophyseal regions can be accomplished via minimally invasive routes with mild adverse effects and very low rates of mortality, the benefits of biopsy in patients with bifocal tumors may outweigh the risks associated with the procedure.

Patients who are hesitant to proceed with a biopsy of a single site should be counseled as to the potential risks and benefits of such an approach. If patients refuse biopsy or the risks of biopsy are felt to be significant, the clinician and patient must weigh the potential risks of biopsy against the risks and likelihood of tumor misclassification. Patient age may guide management in such scenarios, as younger age suggests NGGCT, while older age is more consistent with germinoma.1 Patients who do not undergo biopsy should be considered for repeat serum and possibly CSF tumor markers. Whether patients should undergo a biopsy of both the pineal and neurohypophyseal regions is debatable and should be considered on a case-by-case basis after thorough discussion of the potential risks and benefits with patients and their families.

The main limitation to our study relates to the small sample size. As a result, estimates of frequency of nongerminomatous bifocal tumors derived from our case series are undoubtedly associated with wide confidence intervals when applied to the population at large. However, the main purpose of the study is to establish that NGGCTs can present in a synchronous bifocal fashion with detectable hCG and normal or modestly elevated AFP levels, and we believe that our study has the potential to promote consideration of biopsy in such patients. In conclusion, this is the first study to show that NGGCTs can present in a bifocal manner in the setting of detectable hCG and normal or modestly elevated AFP levels. We found a considerable percentage of NGGCTs in our cohort of patients with bifocal tumors. Due to significant differences in the prognosis and management of germinoma and NGGCT, misclassification of an NGGCT as a germinoma could carry serious clinical consequences, and biopsy should be strongly considered in such patients. Additional studies should further investigate this important finding.

Acknowledgments

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