Presentation of central nervous system sarcoidosis as intracranial tumors

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Five cases of sarcoid presenting as an intracranial tumor are reported. In one instance, the lesion presented as a tumor in the cerebellopontine angle, a site not previously reported for the initial presentation of sarcoid isolated to the central nervous system. The role of computerized tomography, surgery, and steroid therapy is discussed. In the absence of pulmonary involvement, serum angiotensin-converting enzyme levels do not appear to be helpful in predicting steroid response.

KEY WORDS • sarcoid • central nervous system • sarcoidosis • intracranial tumor • granuloma

The dermatological lesions of sarcoidosis were described by Boeck3 in 1899, and in 1905 Winkler28 provided the initial report of the neurological manifestations of this disease. The clinical, radiological, and pathological presentations of systemic sarcoid have been widely reported, but the finding of sarcoid in the central nervous system (CNS) has received much less attention. Delaney16 has presented a comprehensive review of the neurological manifestations of sarcoidosis, and Bahr, et al.,2 and Brooks, et al.,4 have described the neuroradiological presentations of intracranial sarcoidosis.

Sarcoid of the CNS has been variously reported in from 1% to 16% (average 3.5%) of all sarcoid patients.2,10 However, the presentation of sarcoid as an intracranial tumor mass is much rarer. A thorough search of the literature has revealed only 30 such cases, nine of which showed no systemic manifestations of the disease (Table 1). In this paper, we report five additional patients in whom sarcoid presented as an intracranial mass. Three of these patients exhibited no signs of systemic sarcoid at the time of presentation. The relevant neuroradiological and neuropathological findings are reviewed, and current approaches to the management of these lesions are discussed.

Case Reports

A retrospective search of the records of the Baptist Memorial and Kennedy Veterans Administration Hospitals, Memphis, Tennessee, for the years 1980 through 1984 revealed five patients in whom sarcoidosis presented as an intracranial mass lesion. A brief synopsis of these cases with relevant comments follows.

Case 1

This 42-year-old black woman was first evaluated in August, 1983, for a progressive hearing loss over a 6-month period with occasional tinnitus, dizziness, and fasciculations of the left side of the face. She had also noted early morning headaches for several months, but no change in vision. Electrophysiological testing revealed a sensorineural hearing loss suggestive of an acoustic neuroma. The history was remarkable for anosmia without an abnormality of taste, but this complaint was not elicited at the time of presentation. There were no focal deficits of the extremities. No skin lesions were present. Ambulation was normal without ataxia. Cranial computerized tomography (CT) scanning was not performed, but CT cisternography showed a left cerebellopontine angle (CPA) mass (Fig. 1 upper). The cerebrospinal fluid protein level was 119 mg/dl. The patient was discharged home with a tentative diagnosis of CPA meningioma, and plans were made for elective surgery. Upon readmission for tumor removal, a CT scan revealed an enhancing anterior mass lesion involving the floor of the frontal fossa bilaterally. There was moderate parenchymal edema associated with the mass. On the evidence of the CT appearance and the associ-
TABLE 1

Cases of CNS sarcoidosis with no systemic manifestations*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Site of Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aszkanazy, 1952</td>
<td>23, M</td>
<td>temporal lobe</td>
</tr>
<tr>
<td>Case 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skillicorn &amp; Garrity, 1955</td>
<td>19, M</td>
<td>middle fossa</td>
</tr>
<tr>
<td>Goodman &amp; Margulies, 1959</td>
<td>39, M</td>
<td>frontal lobe</td>
</tr>
<tr>
<td>Silverstein, et al., 1965</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>23, M</td>
<td>temporal mass</td>
</tr>
<tr>
<td>Griggs, et al., 1973</td>
<td>18, M</td>
<td>temporal lobe</td>
</tr>
<tr>
<td>Bahr, et al., 1978</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>58, M</td>
<td>temporal lobe</td>
</tr>
<tr>
<td>Lax &amp; Tabaddor, 1979</td>
<td>34, F</td>
<td>frontal lobe</td>
</tr>
<tr>
<td>Brooks, et al., 1982</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>31, M</td>
<td>foramen of Monro, suprasellar</td>
</tr>
<tr>
<td>Case 10</td>
<td>15, M</td>
<td>suprasellar</td>
</tr>
<tr>
<td>Clark, et al., 1985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>42, F</td>
<td>olfactory groove, CPA</td>
</tr>
<tr>
<td>Case 2</td>
<td>17, M</td>
<td>temporal lobe</td>
</tr>
<tr>
<td>Case 5</td>
<td>46, F</td>
<td>orbit, suprasellar</td>
</tr>
</tbody>
</table>

* CNS = central nervous system; CPA = cerebellopontine angle.

ated edema, the mass was thought to be an olfactory groove meningioma. In October, 1983, a bifrontal craniotomy was performed for the removal of the mass which grossly appeared to be a fibrous meningioma. Tissue specimens showed necrotizing granulomatous inflammation with perivascular lymphocytes and multinucleated giant cells. The serum angiotensin-converting enzyme level was 45 units/ml (normal range 44 to 125 units/ml). The patient was discharged home to await readmission for removal of the CPA tumor.

On readmission, examination revealed a left facial asymmetry and sensorineural hearing loss. The serum angiotensin-converting enzyme level was still normal at 54 units/ml. The CPA tumor was exposed and appeared to be a fibrous meningioma, much like the lesion in the frontal fossa. Frozen sections revealed granulomatous inflammation consistent with a diagnosis of sarcoidosis, and surgery was terminated. Permanent sections confirmed this diagnosis, demonstrating caseating and noncaseating granulomas with multinucleated giant cells and fibrosis (Fig. 1 lower). Special stains for acid-fast bacilli and fungi were negative. The patient had an uneventful postoperative course and was discharged on a course of prednisone, 40 mg/day.

Comment

This case represents a unique presentation of sarcoidosis as a CPA tumor. It is important to study these lesions systematically, and we have previously emphasized this point. A contrast-enhanced CT scan should have been performed earlier, and would have identified the frontal lesion. In the circumstances of this case, with the presence of the CPA mass, the peripheral facial paresis (often seen with sarcoidosis), the CT scan appearance of the mass, and its gross appearance at surgery, it is easily understood how this lesion could be mistaken for a meningioma.

Case 2

This 17-year-old black youth was first seen in September, 1983, for evaluation of a 2-week history of severe headaches and daily vomiting. He had right periorbital edema and swelling of the lower part of the face on the right. He was drowsy, but otherwise neurologically intact. A CT scan performed at this time showed what was thought to be an infiltrating glioma in the right mesial temporal lobe (Fig. 2 left), and steroid therapy was begun. A chest x-ray film was normal, and there was no palpable lymphadenopathy. The serum angiotensin-converting enzyme concentration was within normal limits at 101 units/ml (normal range 44 to 125 units/ml). A temporal lobe biopsy showed a dense lymphocytic inflammatory infiltrate in the Virchow-Robin spaces. No noncaseating granulomas or multinucleated giant cells were noted. All cultures and stains were negative for Herpes simplex or other vi-
CNS sarcoid presenting as tumor

ruses. The patient’s steroid therapy was continued until reexamination in March, 1984. The serum angiotensin-converting enzyme level at this time was 46 units/ml, still within normal limits. A CT scan showed resolution of the enhancing mass. When steroid therapy was tapered and eventually discontinued, headaches reappeared and a suprasellar inflammatory mass was identified on CT scanning. This mass responded to prednisone therapy, and resolved within 3 months (Fig. 2 right). The patient continues to receive 20 mg prednisone every other day.

Comment

It is important to realize that sarcoid granuloma can cause gliosis in the surrounding brain parenchyma. The CT appearance may mimic the changes seen with glial tumors, and adequate sampling must be carried out at biopsy in order to assure a proper diagnosis. Unfortunately, needle biopsy is often inadequate since the granulomas are often widely dispersed, and a single biopsy may not include pathological tissue. In spite of inadequate tissue sampling, this patient was presumed to have sarcoidosis on the evidence of his age, race, the presence of an intracranial inflammatory mass, and response to steroid therapy.

Case 3

This 27-year-old black man was diagnosed as having sarcoid on the basis of liver and lymph node biopsies in June, 1981. In September, 1983, he presented with a new grand mal seizure disorder. A CT scan at that time showed an enhancing mass in the supracallosal area (Fig. 3 upper left). He was started on a regimen of Dilantin (phenytoin), 300 mg/day, and prednisone, 20 mg every other day, and there was no further witnessed grand mal activity. He was again seen in June, 1984, complaining of frequent left frontal headaches, anosmia, blurred vision when looking to the left, dizziness, and easy fatigability. He also reported two episodes of loss of consciousness during the preceding year, with the last one in the month prior to admission. A CT scan performed at this time again revealed a supracallosal area of enhancement, which had increased in size since the last CT scan. An open biopsy was then performed in order to confirm the diagnosis of sarcoid. The specimen showed aggregates of epithelioid histiocytes with rare interspersed multinucleated giant cells and peripheral lymphocytic infiltration (Fig. 3 lower). The adjacent brain was edematous and congested, with areas of reactive gliosis and increased vascularity. The patient continued to take Dilantin and prednisone, and has experienced no further neurological deterioration in the months since biopsy (Fig. 3 upper right).

Comment

The recognition of the presence of intracranial masses in a patient with systemic sarcoidosis should cause the physician to be suspicious of their etiology.


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Fig. 4. Serial computerized tomography scans of the orbits in Case 4, showing enlargement of the optic nerve (A), nodularity of the optic nerve (B), and a nodular mass within the globe (C).

Case 4

This 16-year-old black youth had the sudden onset of blurred vision in his right eye in November, 1979. When examined, he was noted to have diffuse palpable adenopathy; he had had this for as long as he could remember. A chest x-ray film showed hilar adenopathy. Examination of the ocular fundus revealed a blurred whitish-gray retina, but the examiner was unable to focus fully on the optic nerve head. A conjunctival biopsy revealed a noncaseating granuloma, and treatment with prednisone, 30 mg/day, was begun. There was some immediate improvement in vision in the right eye, but this stabilized with a residual blurring of vision. A CT scan performed at this time showed multiple nodules on the right optic nerve (Fig. 4). Serum angiotensin-converting enzyme was increased to 75 units/ml (normal range 12 to 36 units/ml). The patient was readmitted for management of respiratory difficulty in April, 1980, and underwent scalene node biopsy which showed a noncaseating granuloma. He did well until May, 1983. At that time he again complained of decreased vision. A chest x-ray film was normal. The serum angiotensin-converting enzyme level was further elevated to 147 units/ml (normal range 44 to 125 units/ml). A CT scan showed an increased area of enhancement at the junction of the retina and optic nerve on the right. The patient was started on a course of prednisone, 30 mg every other day. Follow-up monitoring to date has not revealed a significant change in his visual status or increased intracranial enhancement on CT scanning.

Comment

This case demonstrates that serum angiotensin-converting enzyme levels are not predictive of steroid response in all cases, since these levels continued to increase in spite of clinical improvement in this patient.

Case 5

This 46-year-old black woman presented in 1980 with progressive deterioration of vision in the right eye. She had an obvious proptosis, and a CT scan showed a large mass in the right orbit. A chest x-ray film was normal and there was no lymphadenopathy. Exploration of the orbit revealed nonspecific inflammatory changes and fibroadipose tissue. Visual loss progressed in the right eye in spite of high doses of steroids, and the orbit was re-explored in 1981. The serum angiotensin-converting enzyme level was within normal limits at 64 units/ml. Biopsies of the right optic nerve revealed marked infiltration of the nerve by noncaseating granulomas. Special stains for acid-fast bacilli and fungi were negative. The patient was started on a course of prednisone, 50 mg/day. Over the next year, her vision continued to deteriorate, now in the left eye as well. A CT scan performed then showed an enhancing mass in the apex of the right orbit. There was also a diffuse enhancement in the sellar region with suprasellar extension. She was given methylprednisolone, 1 g/day for 3 days, and then started on prednisone, 80 mg/day, with resulting marked improvement in vision. A follow-up CT scan in 1984 revealed resolution of the suprasellar extension. At present her vision is stable and she continues to do well.

Comment

This patient demonstrates the importance of adequate tissue sampling at the time of surgery. The normal angiotensin-converting enzyme levels in this case would appear to support the contention that this test is of little value in predicting steroid response in patients with CNS sarcoidosis.

Discussion

Judging from the small number of reported cases in the literature, it is rare for sarcoidosis of the CNS to present as an intracranial tumor. Systemic manifestations of sarcoidosis are often present in these patients and should lead to its inclusion in the differential diagnosis. In some cases, however, no systemic signs of sarcoidosis are found initially. Since these granulomas are often associated with variable degrees of meningeal fibrosis and parenchymal gliosis,19 and have been mistaken for meningiomas8,20 or gliomas,22 it is important for neurosurgeons to keep this entity in mind.

Many of the cases of isolated CNS sarcoidosis presenting as a tumor mass were reported in the years before CT scanning was available.1,8,12–14,16,21,24,25 The
diagnosis of CNS sarcoid granulomas is still based on histopathological studies, but CT scanning has had an impact upon the findings and management of these lesions. There is no doubt that high-resolution CT scans aid in the diagnosis of an intracranial sarcoid mass. However, the radiological appearance is quite variable and does not permit distinction from neoplasms or other granulomatous diseases. The best use of CT in these cases may be to follow the patient with serial scans during treatment to document any responses to therapy or exacerbations.

The presentation of CNS sarcoidosis in the absence of systemic signs of the disease is well documented. Some investigators believe that the absence of sarcoidosis in other systems at the time of presentation is not surprising in view of the fact that neuraxis sarcoidosis tends to occur late in the course of the disease after coexisting multisystem lesions have "burned out" and are not easily detected. If this were the case, necropsy should demonstrate multisystem involvement. In fact, investigation at necropsy in several of these patients failed to detect sites of involvement other than in the CNS. An alternative explanation might be that preexisting asymptomatic lesions in other systems have resolved by the time the late-occurring CNS lesions become symptomatic. This issue remains unsettled, and is still a matter of controversy.

The proper strategy for patient management is also controversial. There is no confirmation in the literature that steroids affect the rate of response, because there are reports of lesions that have resolved both spontaneously and with steroid therapy. On the other hand, some sarcoid granulomas are resistant to therapy, and surgery has been necessary to confirm the diagnosis and, in the presence of increased intracranial pressure, to debulk the granulomatous mass. Many sarcoid granulomas can resolve with steroid therapy alone. However, it may be exceedingly difficult to predict accurately a response to steroids or other therapy.

In recent years, the serial measurement of angiotensin-converting enzyme levels in peripheral blood has been used as a prognosticator of steroid response. The blood level of this enzyme is elevated in 70% to 80% of patients with pulmonary sarcoidosis, which is believed to be the result of an increased rate of angiotensin-converting enzyme synthesis by epithelioid cells of the sarcoid granulomas and release of the enzyme into the blood stream. The blood levels of angiotensin-converting enzyme are thought to reflect the total mass of sarcoidosis epithelioid cells, and reduction in the levels of the enzyme may indicate remission and response to therapy. Unfortunately, there have been so few cases of sarcoidosis isolated to the CNS that the association between peripheral angiotensin-converting enzyme levels and granulomas within the CNS is unknown. Our experience indicates that, in the absence of pulmonary involvement, angiotensin-converting enzyme levels are of no proven benefit in the management of CNS sarcoidosis.

For the present, it appears that the preferred management strategy for these lesions depends upon the presence or absence of accompanying systemic sarcoidosis. In patients known to have systemic sarcoidosis and in the absence of any signs or symptoms of increased intracranial pressure, a trial of steroid therapy should be started. Long-term therapy may be necessary, and these patients should be followed at 3- to 6-month intervals with CT scanning to document any therapeutic response. If long-term steroid therapy fails or the patient deteriorates neurologically, a confirmatory tissue diagnosis should be obtained in order to rule out a CNS neoplasm. In patients with increased intracranial pressure, it may be necessary to debulk the granulomatous mass.

The best advice for neurosurgeons is simply to be aware that this entity can occasionally present much like a primary tumor of the CNS without any of the systemic manifestations of sarcoidosis. The diagnosis is based on histopathological tissue sections obtained at surgery. The necessity for a tissue diagnosis before other therapies and their concomitant risks are undertaken is again emphasized.

Conclusions

Five cases of CNS sarcoidosis presenting as an intracranial tumor have been described. Three of these showed no signs of systemic involvement at the time of presentation. We emphasize that a high level of suspicion on the part of the neurosurgeon is the key to making this diagnosis. We conclude that:

1. CT scanning is a valuable adjunct both in the initial diagnosis and in the long-term follow-up monitoring of patients with these lesions;
2. the granulomatous nature of these tumor masses can only be confirmed by tissue sampling;
3. isolation of sarcoid to the CNS, the failure of steroid therapy, or increased intracranial pressure are all indications for surgical intervention: surgery is useful not only for obtaining tissue for making a definitive diagnosis, but also for the debulking of the granulomatous mass in patients with increased intracranial pressure;
4. angiotensin-converting enzyme levels have not proven valuable in following lesions without systemic involvement; and
5. many of these lesions respond to high-dose steroid therapy, and at least a trial is probably advised in the absence of specific contraindications.

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References