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Why Is This Auntminnie a Diagnostic Conundrum?: A Knowledge-Based Approach to Balo's Concentric Sclerosis From Reports of 3 Cases and Pooled Data From 68 Other Patients in the Literature

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Introduction: We came across 3 cases of Balo's concentric sclerosis (BCS). The first of these patients presented to an outside hospital and was transferred to our institution due to complications resulting from a biopsy. The other 2 patients, despite having a characteristic imaging appearance and despite insistence on our part on the diagnosis of BCS, underwent a surgical procedure, which could have been prevented. This led us to review the available literature on BCS.
Material and Methods: A total of 68 patients diagnosed with BCS between 1995 and 2015 were studied and the data collected for the clinical presentation and course, imaging, spinal fluid analysis, treatment, and clinical and imaging outcome.
Conclusions: A 25% surgery rate (biopsy or resection) was found in the study. We concluded that this relatively high surgery rate in this auntminnie nonsurgical disease is multifactorial; and includes factors like nonfamiliarity with the disease, anxiety on the part of patients and physicians, due to a sometimes rapidly deteriorating clinical picture; and resemblance of the disease with other entities such as tumor and infection. However, characteristic imaging appearance combined with acute or subacute presentation and dramatic improvement in clinical status after high-dose steroid chemotherapy; are highly suggestive of the disease, and can prevent unnecessary surgery.

Introduction

Balo's concentric sclerosis (BCS) is a demyelinating disease, considered to be a variant of multiple sclerosis (MS). Many researchers, however, consider the possibility of this being a separate demyelination syndrome.[1-3] It constitutes the spectrum of distinct demyelinating diseases which also includes tumefactive demyelination, Marburg disease, Schilder disease, and acute hemorrhagic leukoencephalitis.[2] The feature of BCS which makes it unique is the presence of lamellated concentric or whorled appearance on T2WI and concentric pattern of enhancement on post-Gd T1WI.[2-4]

We collected data on clinical presentation, disease course, imaging, spinal fluid analysis, treatment, and outcome in 68 patients diagnosed with BCS in the literature, after we came across 3 patients in our department with the characteristic imaging findings, in 2 of which surgical approach was used for treatment and diagnosis, in spite of our assertion on BCS. We found in the literature that a fourth of patients with BCS had undergone some kind of surgical procedure. This, in our opinion, is a high proportion, considering BCS has a typical imaging appearance. Clinical presentation, course of disease and response to high-dose steroids can aid in arriving at the accurate diagnosis and can reduce surgical rates.

Case 1

A 36-year-old man presented to an outside hospital on 5/15/2010 with an acute onset of right-sided weakness, which had progressively worsened in the past 2 days. A computed tomography and magnetic resonance imaging (MRI) was done and a left frontal lobe lesion was found, which was biopsied at the outside hospital. The patient was transferred to our hospital due to postoperative complications of progressive right-sided weakness and increased hemorrhage into the surgical cavity. On review of the outside MR images, a well-defined rounded lesion was found in the left frontal white matter with a concentric appearance and alternating layers of hypo and hyperintensity on T2, fluid attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) images (Fig 1A-C). There were concentric layers of enhancement on post-Gd images (Fig 1D and E). No additional lesions were found. Pathology slides reviewed at our institution showed presence of axons that lacked surrounding myelin associated with reactive gliosis, supporting a diagnosis of tumefactive demyelinating lesion. The patient was placed on high-dose steroids. The remainder of the postoperative period remained uneventful. Follow-up imaging showed that the biopsy and the resultant hemorrhage into the cavity (Fig 1F) had caused an area of porencephalic encephalomalacia in the subcortical white matter of the left precentral gyrus and in the left corona radiata with Wallerian degeneration of the corticospinal tract. Until the most recent clinical follow-up, the patient continues to have profound right hemiparesis. Follow-up imaging 4 years after the surgery continues to show the area of encephalomalcia (Fig 1G) without appearance of new lesions.

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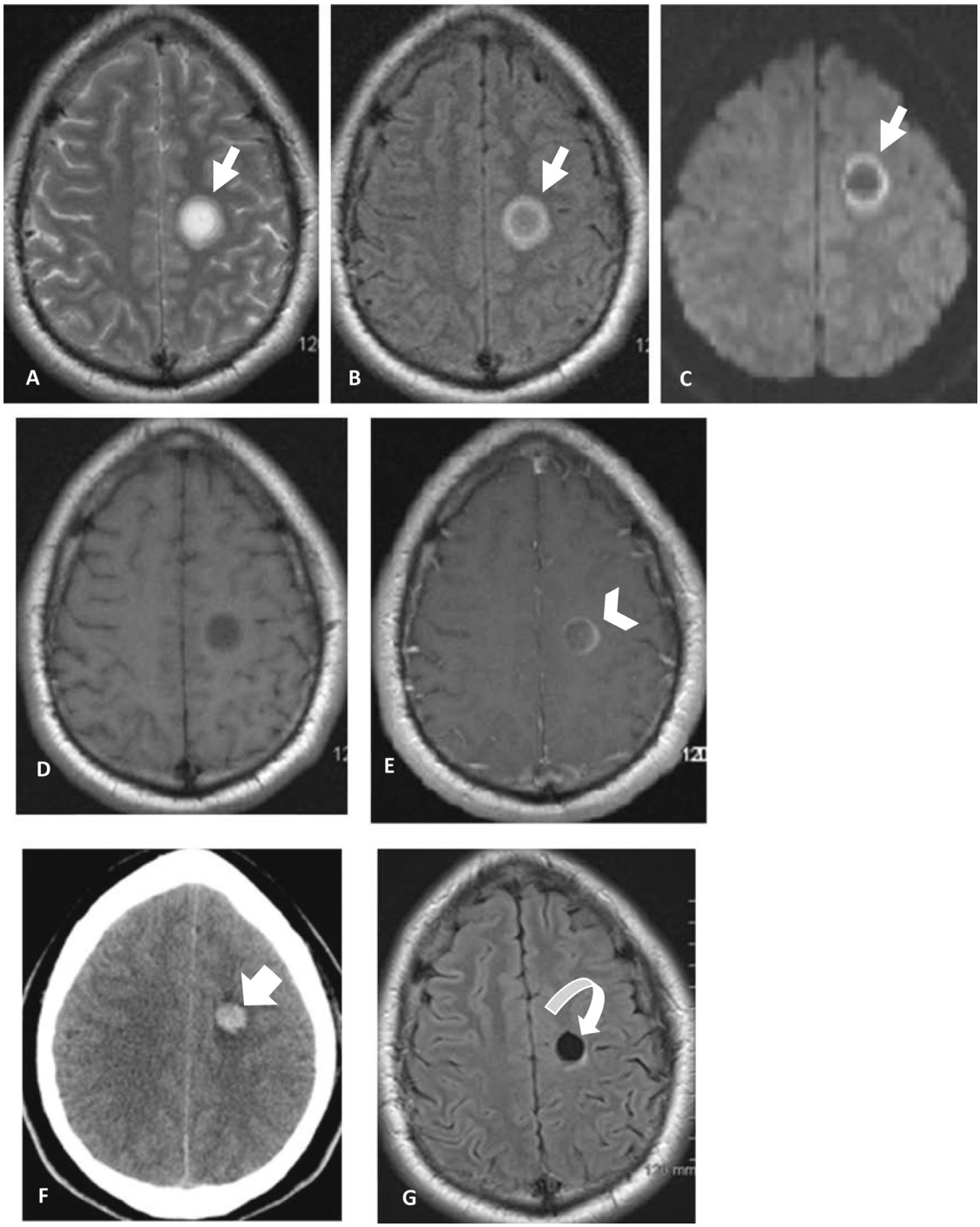

FIG 1. (Case 1): A 36-year-old man presenting with acute right-sided weakness. Axial T2W (A), FLAIR (B), and DWI (C) MRI images showing the typical concentric whorled appearance of Balo's concentric sclerosis in the left frontal white matter or corona radiata (white arrows). Axial precontrast T1W (D) and postcontrast (E) images show concentric layers of enhancement (chevron in E). Axial noncontrast postbiopsy CT image (F) shows hemorrhage into the surgical cavity (thick white arrow). The 4-year follow-up Axial FLAIR MRI image (G) shows the surgical cavity in the left corona radiata (curved white arrow). No new or additional lesions were found. CT, computed tomography.

Case 2

A 52-year-old woman presented on 5/29/2013 with 1 week of acute and progressively worsening language difficulty. Computed tomography head at the emergency department revealed a low attenuation left frontal subcortical white matter lesion with suspicion raised for a primary or secondary brain neoplasm. Hematological analysis was unremarkable for infectious or inflammatory markers. With the provisional diagnosis of a brain neoplasm, a contrast-enhanced MRI and functional imaging was performed for presurgical evaluation. MRI revealed a well-defined rounded T1 hypointense and T2 and FLAIR hyperintense lesion in the left corona radiata (Fig 2A, B, and D). On the long TR images, the lesion had a concentric appearance with alternating bands of hypointensity and hyperintensity. Somewhat concentric appearance was also noted on DWI images (Fig 2C). An incomplete ring of peripheral enhancement was noted (Fig 2E). Scattered small foci of nonspecific long TR hyperintensity were noted in the right periventricular white matter. MR spectroscopy showed a choline peak with reversal of the NAA/Cho ratio, as well as a prominent lipid or lactate peak (Fig 2F). Mean

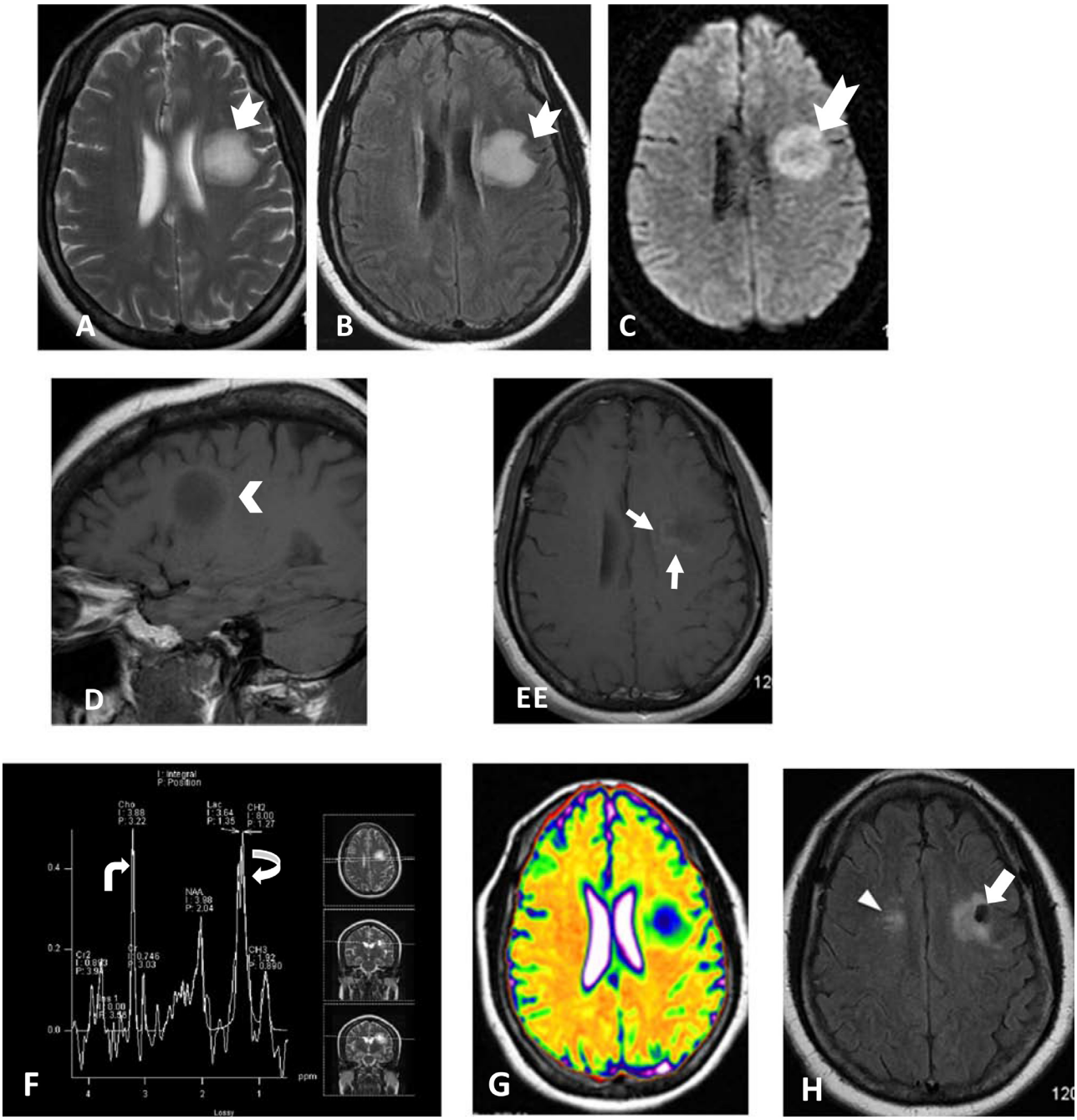

FIG 2. (Case 2): A 52-year-old woman with acute onset of rapidly progressive language difficulty. Axial T2W (A) and FLAIR (B) images show a well-defined lesion in the left periventricular corona radiata (small notched arrows) with concentric layers of hyperintensity and hypointensity. Axial DWI (C) image shows a somewhat whorled lesion with restricted diffusion (long notched arrow). Sagittal precontrast T1W image (D) shows a well-defined hypointense lesion. Peripheral zone of hyperintensity on T1WI is typical of demyelinating lesions (chevron in D). Axial postcontrast T1WI (E), shows incomplete arc of peripheral enhancement (small white arrows). MR spectroscopy image (F) shows elevated choline (bent arrow) with increased Cho/NAA ratio. Increased lipid or lactate peaks (curved arrow) are also seen. Findings are nonspecific and may be confused with high-grade neoplasm. MRI mean diffusivity (MD) maps (G) show the left corona radiata lesion with a centrifugal pattern of diffusivity with the maximum diffusivity seen centrally. A concentric pattern is also appreciated on the MD maps. Three-year follow-up axial FLAIR MRI image (H) shows the biopsy cavity with decreased lesion size in the left corona radiata (thick arrow). Small hyperintense lesions oriented perpendicular to the right ventricular surface (arrowhead) are more conspicuous in the interim.

diffusivity images showed a centrifugal diffusivity pattern with maximum diffusivity in the central portion of the lesion (Fig 2G). The radiological diagnosis now was reported to be consistent with tumefactive demyelination or Balo concentric sclerosis. Meanwhile, the patient was put on 4 mg dexamethasone tid, but her language difficulty worsened progressively. A spinal fluid analysis failed to show oligoclonal bands. A decision was made to biopsy the lesion. Histology showed multiple foci of incomplete myelin loss alternating with preserved myelin on Luxol fast blue stain consistent with a pattern of BCS. The patient was then put on 1 g Solumedrol iv daily. The patient improved gradually with some residual language difficulty on her last hospital visit in April 2016. She however did complain of nonspecific vision abnormality with intermittent nystgamus. Serial follow-up MRI scans have shown decreasing size of the left frontal lesion (Fig 2H). The right periventricular white matter lesions have however become increasingly more conspicuous and are reminiscent of MS on the most recent study (Fig 2H). No optic nerve lesions have been found.

Case 3

A 56-year-old man presented on 8/27/2013 with acutely progressive left hand weakness and spasticity. MRI of the brain revealed a well-defined ~3 cm perirolandic subcortical lesion with concentric appearance on long TR images and with an incomplete peripheral ring of enhancement (Fig 3A-D). There was lack of mass effect. Mean diffusivity maps showed a centrifugal pattern of diffusivity (Fig 3E). Arterial spin labeling showed no areas of abnormal increased perfusion. Two small nonspecific foci of abnormal T2 and FLAIR hyperintensity were seen, 1 each in bilateral corona radiata. Radiological appearance was reported consistent with tumefactive demyelination or BCS. Cerebrospinal fluid (CSF) studies showed protein of 35 mg/dL and 6 oligoclonal bands (normal 0-3). A biopsy of the lesion was nevertheless performed with the cited reason being "rapidity of loss of function of hand." Amber colored fluid was expressed from the

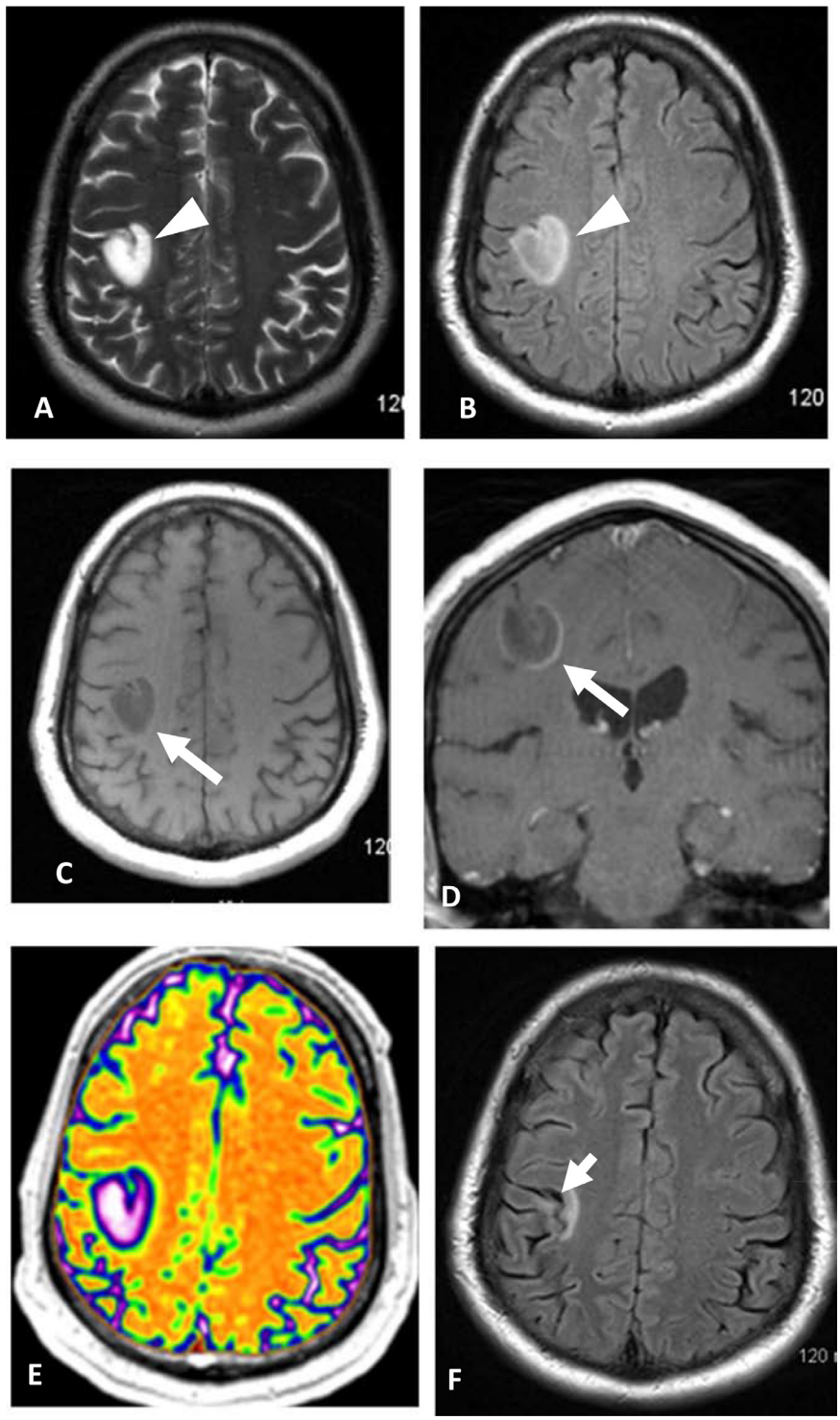

FIG 3. (Case 3): Axial T2W (A) and FLAIR (B) MRI images show a well-defined hyperintense lesion with a concentric pattern in the right perirolandic region (arrowheads). Axial precontrast (C) and coronal post-Gd (D) T1W MRI images of the brain show incomplete peripheral enhancement (long arrows in C and D). Axial mean diffusivity maps (E) show centrifugal pattern of diffusivity in the right perirolandic lesion with maximum diffusivity seen centrally. Three-year follow-up axial FLAIR MRI (F) shows significant resolution of the right perirolandic lesion (small arrow). No interval lesions were found.

TABLE 1
Age distribution of patients

Age range	No. of patients
1-10	3
11-20	8
21-30	20
31-40	17
41-50	10
51-60	10

lesions and multiple specimens obtained. Pathology reported a lymphohistiocytic inflammation with relative axonal preservation and myelin loss, consistent with a demyelinating process. The patient was put on 1 g Solumedrol iv daily. The postoperative period was uneventful. On his most recent visit in August 2016, the left hand weakness had improved. He however had focal toni-clonic seizures in his left hand without spread, which were decreasing in frequency. The patient is currently on antiseizure medication. The most recent MRI showed resolved lesion in the perirolandic region (Fig 3F). Imaging sequelae of biopsy were seen. The 2 small nonspecific long TR hyperintense lesions were unchanged.

Study of 68 BCS Patients in the Literature

Methods

A total of 68 patients diagnosed with BCS, published in the literature between 1995 and 2015 were studied. Data were collected for the clinical presentation, clinical course, imaging, spinal fluid analysis, treatment, and outcome.

Results

Demographics

There were 44 females and 24 males. This female sex predilection is in accordance with prior studies.[5,6] The patients ranged in age from 4.75 years to 58 years. The largest number of patients were within 21-40 years age range (37 patients) (Table 1).

No mention of patient ethnicity was made in the literature in 32 patients. Within the identified ethnic groups, 22 were Asian (including Chinese, Japanese, Korean, Taiwanese, Malaysian, and Indian), 9 were white, 3 African-American, and 2 Middle-Eastern. The high prevalence of disease in the Asian population is supported by other studies.[3,7,8] In our study, however, overestimation or underestimation is possible due to the large number of patients with unidentified ethnicity (Table 2).

Presentation

Of all, 64 of 68 patients had an acute or subacute presentation. Of the 64, 42 had symptom onset ranging from 0-2 days (acute) while 22 had symptom onset ranging from 2-10 days (subacute). Only 4 patients had an insidious onset of 1-2 months. Symptoms were clearly progressive over a few days in 21 patients (Table 3). The most common presenting symptom was right or left hemiparesis and hemianesthesia (43 patients). The range of presenting symptoms are summarized in Table 4.

TABLE 2
Distribution of ethnicity

Ethnicity	No. of patients
Unknown	32
Asian	22
White	9
African-American	3
Middle-Eastern	2

TABLE 3
Clinical presentation

Presentation	No. of patients
Acute (0-2 d)	42
Subacute (2-10 d)	22
Chronic (1-2 mo)	2
Progressive clinical course with worsening in few days	21

CSF Examination

CSF examination was not performed in 29 patients. Out of the 39 patients, in whom CSF examination was performed, 27 did not show oligoclonal bands in the CSF, while in 12 patients oligoclonal bands were present. Among the 12 patients who had oligoclonal bands in CSF, 9 had small T2 hyperintense lesions in the brain. These T2 hyperintense lesions were nonspecific, the differential for which includes MS (MS-like lesions). Among the remaining 3 patients from the group of these 12 patients, 1 developed MS-like lesions on follow-up. None of these 12 patients, however, had known MS (Table 5). These findings suggest the overlap of MS with BCS. It is interesting to note that oligoclonal bands positivity is associated with coexistent MS. As more data becomes available, it is possible that positive CSF examination could be used as a predictor of MS development later in the BCS disease course.[8,9]

Single vs Multiple Lesions and Association With MS

A total of 32 patients had a single lesion while in 36 patients more than 1 lesion with concentric pattern was present. In 31 patients, other scattered lesions which could suggest MS (MS-like lesions) were present. Among them, 6 patients had known MS (62 without known MS). Only 15 patients had a single lesion, without associated nonspecific lesions elsewhere at presentation. A total of 18 patients out of the 62 (without known MS) developed MS-like lesions on follow-up. Of these 18, there were 5 patients who had a single Balo's-like lesion on presentation without associated nonspecific T2 hyperintense lesions. The overlap of Balo with MS had made it difficult to completely separate the 2 and many believe Balo to be a variant of MS.[5,8,10]

TABLE 4
Symptom distribution

Presenting symptoms	No. of patients
Hemiplegia/hemiparesis with hemianesthesia	43
Facial palsy	15
Speech difficulty	21
Monoparesis	6
Quadriparesis	2
Gait disturbance	7
Limb paresthesias	1
Visual field cut	3
Diplopia	1
Memory impairment	6
Altered behavior	2
Impaired consciousness	2
Confusion	1
Cognitive decline	1
Lack of concentration	1
Dysphagia	3
Dizziness	1
Seizures	2

TABLE 5
CSF analysis

Oligoclonal bands	No. of patients		
Absent	27		
Present	12	Nonspecific T2 lesion in brain that may be MS	9
		Developed MS-like lesions on follow-up	1
		No MS-like T2 lesions at presentation or follow-up	2

Lesion Location

The most frequent location for the lesions were the frontal white matter and centrum semiovale, followed closely by parietal and fronto-parietal white matter and corona radiata. Lesions were less frequent in occipital, temporal, parieto-occipital, and temporo-occipital white matter regions, and in the periventricular regions. Only 1 patient had lesions in bilateral thalami. This is in consistence with prior studies which report the most common location for BCS to be the cerebral white matter.[2,8] There is relative sparing of cortical grey matter and the subcortical U fibers.[2,8]

Imaging Appearance

Concentric, lamellate or "onion-peel" is the characteristic and defining appearance of BCS lesions and is one that differentiates this from other demyelinating lesions. Descriptions vary from 1 or 2 to several alternating bands of demyelination and lesions can vary in size from no more than a centimeter to a substantial portion of a cerebral hemisphere.[2]

A total of 57 patients showed concentric T2 hyperintense rings on imaging. Among them, 45 out of these 57 patients showed either a concentric pattern of enhancement or peripheral incomplete ring enhancement. In 7 of 57 patients, contrast was not administered and in 5 of the 57 patients enhancement was not seen. In 11 of 57 patients showed a peripheral rim of restricted diffusion or concentric rings of restricted and unrestricted diffusion. In 3 patients out of the total 68, the appearance of the lesion was described in the article as being "typical" of Balo. These articles, however, did not show the images. In 1 patient, the images were postmortem and were described as being "floral." In 1 patient, the images were described as "lamellated" instead of "concentric." In 6 patients, the lesions were not typically concentric, but presented as areas of ill-defined T2 hyperintensity. Among 4 of these 6 patients showed a concentric or incomplete ring appearance after contrast administration. In 2 patients, the lesions started as vague areas of T2 hyperintensity but developed a concentric appearance later in the course of disease.

Advanced Imaging Techniques

MR Spectroscopy

Spectroscopy data was available in 17 patients. All patients showed a choline peak and decreased NAA. A total of 12 patients also showed a lipid or lactate peak.

Mean diffusivity

Diffusivity maps were not used in the cases studied in the literature. In the 2 cases seen at our institution, centrifugal diffusivity pattern was seen with the maximum diffusivity at the center of the lesion.

Arterial Spin Labeling

ASL patterns were also not studied in the cases found in the literature. Our cases showed hypoperfusion within the lesions, a pattern that can be useful in differentiating BCS from neoplasms or infective lesions.

Surgical Intervention—Biopsy or Resection

In all, 17 patients underwent a biopsy procedure to establish a diagnosis (Table 6). In 2 patients, a biopsy was planned but not done (patient refused surgical intervention in one of these). Of the 17 who underwent biopsy, 6 had a single lesion at presentation without associated nonspecific T2 hyperintense lesions. In 15 patients, primary or metastatic brain neoplasm was in the differential diagnosis. However, 2 patients in whom neoplasm was suspected, a biopsy was not performed, leaving 13 patients, where a biopsy was truly done to rule out neoplasm. In the 2 patients where neoplasm was suspected but biopsy was not done, the patients were given a trial of high-dose steroids, to which they responded and biopsy obviated. All 6 patients in whom there was a single lesion at presentation without associated T2 lesion and a biopsy was performed, neoplasm was in the differential diagnosis. There were 4 patients who underwent biopsy, without neoplasm in the differential diagnosis. Only 1 patient underwent subtotal resection.

It is interesting to note that a lesion that has a very characteristic imaging appearance has a biopsy rate of as high as 25%. We also looked into the temporal pattern of biopsies over the years. There were 32 studies before 2005 and 36 studies after 2005. Surprisingly, the biopsy rate remained at 25% for both groups ie, 8 patients before 2005 and 9 patients after 2005.

Ethnicity remained unknown in about half of the patients but it appeared that surgical intervention or biopsy was more common in the non-Asian group of patients.

Clinical Course and Response to Treatment

Total of 17 patients responded very well to high-dose corticosteroid therapy and were documented to recover fully, without residual deficits (Table 7). Another 33 patients showed good response to therapy and recovered with minor deficits, which did not affect their daily life in a significant manner. In 3 patients, the clinical recovery was partial with moderate residual deficits. In 2 patients, the clinical course was progressively worse over several months, with 1 patient still in active phase with frequent relapses. Another patient progressed to quadriplegia. Two patients succumbed to the lesions even after aggressive steroid and immunosuppressive therapy. In 9 patients, clinical follow up was not given but imaging follow-up showed reduced size and enhancement of the lesion, with change in morphology. In 2 patients, clinical or imaging follow up was not done. Of all, 16 patients showed relapse of disease, either in the form of full-blown MS, tumefactive demyelination, or Balo lesions. In 20 patients, enough follow-up data were not available.

Discussion

First described as encephalitis periaxialis concentrica in 1928 by Josef Balo, BCS is a relatively uncommon demyelinating disease characterized by concentric layers of demyelination and relatively

TABLE 6
Surgical intervention

	No. of patients
Total no. of patients who underwent biopsy	17
Biopsy planned but not done	2
Biopsy performed on single lesions	10
Biopsy performed on single lesions without associated MS-like lesions	6
Biopsy performed to rule out neoplasm	13
Neoplasm suspected	15
Neoplasm suspected but steroid trial given	2
Biopsy performed but tumor not in the Ddx	4
Subtotal resection	1

TABLE 7
Clinical course and response to therapy

	No. of patients
Very good response to high-dose corticosteroid therapy with complete clinical recovery	17
Good response to therapy with mild residual deficits causing no significant effect on daily life	33
Clinical recovery but moderate residual deficits	3
Progressively worse clinical course on therapy	2
No mention of clinical course but reduced size and enhancement of lesion on imaging follow-up	9
Patient demise	2
No follow-up	2
Relapse	16

preserved myelin in large white matter areas in the brain. It is more common in females[5,6] and in people of Asian origin.[3,7,8] A number of etiologic factors have been speculated which include autoimmunity,[8] environmental factors,[2] and infection.[11,12]

The classic concentric appearance of BCS is most conspicuous on T2W and FLAIR images with alternating layers of hyperintensity and hypointensity, and a central hyperintense core. There can be 1 or 2 to several alternating bands.[2] The concentric appearance may or may not be evident on T1W images. DWI images may show the concentric pattern or zone of peripheral hyperintensity.[13,14] Postcontrast T1W images show a peripheral, usually incomplete ring of enhancement; although a concentric pattern of enhancement is not unusual.[15,16] MR spectroscopy may show an increase in the choline to NAA ratio, and an increase in lipid and lactate.[17,18] Susceptibility-weighted imaging may show microhemorrhages and ectatic veins in T2 hyperintense regions, findings which may support the view that vascular pathology plays a role in BCS imaging.[19] Positron-emission tomography imaging shows no 2-[fluorine 18]fluoro-2-deoxy-D-glucose uptake.[18]

There has been recent interest in diffusivity patterns in demyelinating lesions including BCS. In the cases imaged at our institution, we found a centrifugal pattern of mean diffusivity, with maximum diffusivity seen at the central portion of the lesion. This is in consistence with studies done on MS patients where a similar pattern of mean diffusivity was noted.[20,21] A centrifugal pattern of apparent diffusion coefficient values was noted in a study on 18 BCS lesions.[22] This newer imaging technique, thus has value in early detection and can add specificity to BCS lesions.

Microscopically, the concentric appearance is found to be due to alternating zones of myelin loss and relative myelin preservation. There is relative axonal sparing. The epicenter of the lesion appears to be a perivenular zone where the inciting chemical mediator induces demyelination and spreads successively outward in waves. A unique interplay between hypoxia-induced tissue preconditioning and proinflammatory cytokines derived from glial cells may contribute to the development of the concentric pattern.[23,24]

Previously considered lethal, BCS cases can now be diagnosed earlier with MRI and treated with complete recovery or minor residual deficits in the majority of cases with high-dose steroids, immunotherapy, or plasmapheresis. Aggressive lesions may however still cause death or leave the patients with significant morbidity.

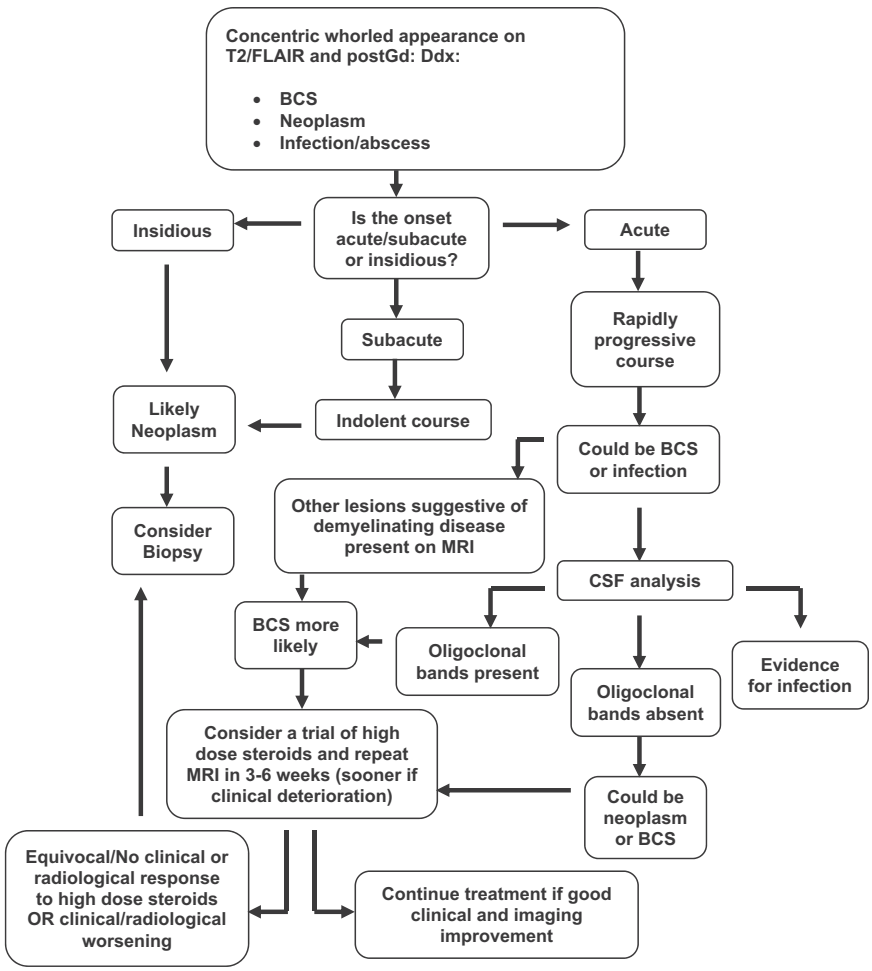

FIG 4. Algorithm to approach a case of suspected Balo's concentric sclerosis.

Conclusions

Whorled, concentric, or lamellated appearance in large white matter areas is an auntminnie appearance of BCS and is one that differentiates this from other entities. Despite the characteristic appearance (seen in 100% cases at some point in the disease course), a fourth (25%) of these patients are biopsied, a rate that has been shown to be constant in our study over the years. Most patients biopsied have the differential diagnosis of a tumor. However, 97% cases in our study had an acute or subacute presentation, with 30% showing an acutely progressive decline; a clinical feature rarely, if at all, seen in patients with a tumor. Also, rapid response to high-dose steroid therapy, which includes a change in imaging appearance of the lesion (seen in 87% cases in the pooled data), is not a feature of neoplasms. It should be noted that the low-dose steroids administered for lessening edema in tumor patients are not effective in BCS and although there may be improvement in symptoms due to lessened edema, the lesion remains unchanged after steroid administration. The characteristic imaging appearance combined with the acute or subacute presentation and rapid response to steroids should, in most cases, have pointed to the diagnosis. Nevertheless, 25% cases saw the surgeon's knife.

The 2 cases that we saw in our department gave us some insights into the possible causes for the high biopsy rate. Disease rarity, especially in the western hemisphere, is possibly one of the major causes. There is relative nonfamiliarity among radiologists and surgeons for this disease entity, which brings other, more sinister, differential diagnoses on the table. This combined with the rapidly deteriorating clinical course of the patient, provokes anxiety in the patient and the surgeon, and compels them to get a tissue diagnosis. Relative poor response to the usual low-dose steroid therapy contributes to the anxiety. The proposed diagnosis of a demyelinating lesion further goes awry when the CSF comes back negative for oligoclonal bands, a feature not uncommon in BCS. Only 30% cases of BCS in our pooled data showed positive oligoclonal bands. Neither of our 2 patients tested positive for oligoclonal bands. MR spectroscopy shows a tumor-like profile with elevated choline and lipid or lactate peaks, which adds to the diagnostic conundrum.

However, our analysis suggests that a mindfulness of this disease entity and the characteristic imaging appearance combined with the acute or subacute clinical presentation, and a dramatic change in clinical status after high-dose steroids, should minimize biopsies in this nonsurgical auntminnie diagnosis. We propose the following algorithm to approach cases with suspected BCS (Fig 4).

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