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MAJOR ARTICLE

Clinicodemographic and Radiological Features of Infective Ring-Enhancing Brain Lesions: A 4-Year Retrospective Study at a Tertiary Referral Center

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Background. The diagnostic evaluation of ring-enhancing brain lesions (REBLs) is challenging, especially in immunocompromised patients. We conducted a retrospective study to describe the clinicodemographic and radiological features among patients presenting with REBLs to a tertiary referral center.

Methods. Radiological reports of all patients who underwent brain computed tomography or magnetic resonance (MR) imaging between 1 November 2013 and 31 October 2017 were filtered for terms indicative of REBLs. Infectious diseases physicians reviewed the medical records to confirm the diagnosis.

Results. Over the 4-year study period, there were 42 patients with infective REBLs and 249 with neoplastic REBLs. Pyogenic brain abscesses (PBAs) (20 of 42 [47.6%]) were the most common cause of infective REBLs, followed by tuberculous brain abscesses (TBAs) (9 of 42 [21.4%]) and *Nocardia* brain abscesses (NBAs) (6 of 42 [14.3%]). The patients were predominantly male, with a mean age of 55.2 years. Fewer than half were febrile at presentation. Cerebrospinal fluid investigations established the microbiological diagnosis in fewer than half of those who underwent lumbar puncture or extraventricular drain insertion. Conversely, brain biopsy yielded the microbiological diagnosis in almost all patients (16 of 17) who underwent the operation. Median white blood cell counts and C-reactive protein were higher in those with PBAs or NBAs than in those with TBAs. All with PBAs and NBAs who underwent MR imaging had diffusion-weighted imaging–hyperintense lesions, compared with only about half of those with TBAs.

Conclusions. Our study has revealed important distinguishing features between infective REBLs and neoplastic REBLs and between PBAs, TBAs, and NBAs.

Keywords. *Nocardia*; pyogenic brain abscess; rim-enhancing; ring-enhancing brain lesions; tuberculosis.

Ring-enhancing brain lesions (REBLs), areas of low density or signal surrounded by a bright rim from contrast enhancement on neuroimaging [1], may be due to infective or noninfective causes. In referral centers with many patients who are immunocompromised due to disease and/or treatment, REBLs pose a significant diagnostic challenge as opportunistic infections add to the list of differential diagnoses. Prompt and accurate diagnosis is crucial as patients with central nervous system (CNS) infections can rapidly deteriorate with substantial morbidity and mortality [2, 3]. However, there are limitations with the current diagnostic approaches: clinical presentations may be atypical [4], neuroimaging features can overlap between etiologies [1, 5], and brain biopsy, the reference standard for diagnosis, may not be feasible due to unacceptable surgical risks [6]. We conducted a retrospective study to describe the clinicodemographic and radiological features of patients presenting to a tertiary referral center with REBLs. We also compared the clinicodemographic and radiological features of patients with the 3 most common infective causes—pyogenic brain abscesses (PBAs), tuberculous brain abscesses (TBAs), and *Nocardia* brain abscesses (NBAs)—to identify distinguishing features.

METHODS

The SingHealth centralized institutional review board approved this retrospective study, which was conducted at Singapore General Hospital (SGH). SGH, the largest tertiary referral

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hospital in Singapore, sees a high volume of immunocompromised patients through its hemato-oncology, solid organ and hematopoietic stem cell transplantation, rheumatology, and infectious diseases services.

Radiological reports for all patients who underwent brain computed tomography (CT) or magnetic resonance (MR) imaging at SGH between 1 November 2013 and 31 October 2017 were filtered for search terms indicative of REBLs (Supplementary Data 1). Two board-certified infectious diseases physicians independently reviewed the electronic medical records of the identified patients to verify the final diagnoses and confirm the presence of ≥1 REBL on neuroimages, in consultation with a board-certified neuroradiologist. Institutional review board approval for waiver of patient consent was obtained (CIRB 2020/2520).

Diagnoses were defined as "definite" if an infectious agent or a neoplasm was detected in brain tissue or cerebrospinal fluid (CSF) through cultures, histology, or antigen or molecular testing and the clinical presentation was consistent with the diagnosis. Diagnoses were defined as "probable" if an infectious agent or a neoplasm was detected in blood or extracranial tissue through cultures, histology, and antigen or molecular testing and the clinical presentation was consistent with the diagnosis. Patients whose findings did not fulfill the above criteria for either definite or probable diagnoses were excluded from the study. Relevant clinicodemographic and radiological data were collected for each patient through a comprehensive review of electronic medical records.

Statistical Analysis

For categorical variables, Fisher exact or χ^2 tests were performed where appropriate. Continuous variables were compared using 1-way analysis of variance or z tests where appropriate. Post hoc comparisons were adjusted for multiple testing using the Bonferroni correction. A significance level of .05 was used for all statistical tests. Data management and analysis were performed using Stata statistical software, version 18 (StataCorp).

RESULTS

Over the 4-year study period, 807 unique patients whose brain CT/MR imaging reports contained the search terms were screened. Of these, 291 patients had diagnoses that fulfilled criteria for a definite (n = 105) or probable (n = 186) infective or a neoplastic etiology. Of the 291 patients, 42 (14.4%) had REBLs with an infective etiology and 249 (85.6%) had REBLs with a neoplastic etiology. The infective REBLs were secondary to various microbiological agents, including bacterial, mycobacterial, parasitic, and fungal causes. Specifically, pyogenic bacteria (20 of 42 [47.6%]) were the most common cause of infective REBLs, followed by *Mycobacterium tuberculosis* (9 of 42 [21.4%]), *Nocardia* species (6 of 42 [14.3%]), *Toxoplasma gondii* (3 of 42 [7.1%]), *Taenium solium* (2 of 42 [4.8%]), *Cryptococcus* species (1 of 42 [2.4%]), and *Aspergillus fumigatus* (1 of 42 [2.4%]). All except 4 cases of polymicrobial PBAs were monomicrobial infections. Metastatic lung cancers (115 of 249 [46.2%]) were the most common cause of neoplastic REBLs, followed by primary brain tumors (43 of 249 [17.3%]), metastatic breast cancer (36 of 249 [14.5%]), metastatic gastrointestinal cancers (21 of 249 [8.4%]), and lymphoma (10 of 249 [4.0%]). Table 1 shows the distribution of the causes of both infective and neoplastic REBLs.

Infective REBLs

The mean age (SD) of patients with infective REBLs was 55.2 (14.8) years, and most patients were male (30 of 42 [71.4%]) and Singaporean (38 of 42 [90.5%]) (Table 2). Half (21 of 42) were immunocompromised, and fewer than half (16 of 42 [38.1%]) were febrile at clinical presentation. The median total white blood cell (WBC) count (interquartile range [IQR]) was 9.9 (7.1–13.8) × 10^3/μL and the median C-reactive protein (CRP) level was 59.5 (9.4–133.0) mg/L.

Of the 38 patients with blood cultures, about one-third (14 of 38 [36.8%]) were found to be bacteremic. Pyogenic bacteria were the most commonly isolated infectious agents in blood

Table 1. Specific Causes of Ring-Enhancing Brain Lesions

Cause	No. of Cases
Infective	**42**
Pyogenic bacteria[a]	20
Mycobacterium tuberculosis	9
Nocardia species	6
Toxoplasma gondii	3
Taenia sodium	2
Cryptococcus sp	1
Aspergillus fumigatus	1
Neoplastic	**249**
Lung cancer	115
Primary brain tumors	43
Breast cancer	36
Gastrointestinal cancer	21
Lymphoma	10
Urological cancer	7
Gynecological cancer	4
Soft-tissue cancers	3
Skin cancer (melanoma)	2
Germ cell cancer	1
Oral cancer	1
Unknown primary	6
Total	**291**

[a]Specific microbiological agents identified in the cases of pyogenic brain abscesses included *Klebsiella pneumoniae* (n = 6), *Staphylococcus aureus* (n = 4), *Streptococcus anginosus* (n = 2), *Aggregatibacter actinomycetemcomitans* (n = 1), *Serratia marsescens* (n = 1), *Bacteroides uniforms* (n = 1), *Prevotella baroniae* (n = 1), and polymicrobial (n = 4). The following microbiological agents were identified in the 4 cases of polymicrobial pyogenic brain abscesses: case 1, *Streptococcus intermedius* and *Eikenella corrodens*; case 2, *Fusobacterium* sp and gram-positive bacilli and gram-positive cocci on Gram staining; case 3, *Weisella viridescens* and *Fusobacterium* sp; and case 4, *S anginosus* and *Parvimonas micra*.

Table 2. Characteristics of Patients With Infective Versus Neoplastic Ring-Enhancing Brain Lesions

Characteristic	Patients, No. (%)[a]		*P* Value
	Infective REBLs (n = 42)	Neoplastic REBLs (n = 249)	
Age, mean (SD), y	55.2 (14.8)	61.6 (12.4)	<.001
Male sex	30 (71.4)	129 (51.8)	.02
Singaporean nationality	38 (90.5)	228 (91.6)	.76
Fever as a presenting complaint	16 (38.1)	10 (4.0)	<.001
WBC count, median (IQR), $\times 10^3/\mu L$	9.9 (7.1–13.8)	8.5 (6.5–10.8)	.02
CRP, median (IQR), mg/L	59.5 (9.4–133.0)	12.0 (4.0–90.5)	.048
Multiple REBLs	29 (69.0)	150 (60.2)	.31
Hydrocephalus	12 (28.6)	12 (4.8)	<.001

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; REBLs, ring-enhancing brain lesions; WBC, white blood cell.

[a]Data represent no. (%) of patients unless otherwise specified.

cultures (11 of 14 [78.6%]), and *Klebsiella pneumoniae* (n = 4) and *Staphylococcus aureus* (n = 3) accounted for more than half of the cases. Two patients who were undergoing chemotherapy for leukemia were found to have *Nocardia* bacteremia, while a patient with newly diagnosed advanced human immunodeficiency virus (HIV) infection was found to have *M tuberculosis* bacteremia.

Thoracic CT was performed in 32 patients with infective REBLs. Radiological findings, such as miliary nodules and cavitary pneumonia, provided clues to the diagnosis in almost three-quarters of these patients (71.8% [23 of 32]).

CSF was sampled in 15 patients: 9 via lumbar puncture (LP) and 6 via external ventricular drainage (EVD). CSF pleocytosis (defined as cell count $>5/\mu L^3$) was present in fewer than half of patients (6 of 15 [40.0%]). Similarly, CSF investigations yielded a microbiological diagnosis in fewer than half (6 of 15 [40.0%]) of the patients—3 with tuberculosis and 1 each with *K pneumoniae* infection, toxoplasmosis, and cryptococcosis. Of the 2 patients with cerebral toxoplasmosis who had CSF sampled, toxoplasma DNA was detected with polymerase chain reaction in brain tissue but not CSF in 1 patient.

About half (20 of 42 [47.6%]) of the patients with infective REBLs underwent brain surgery for diagnostic and/or therapeutic purposes. Brain biopsy yielded the microbiological diagnosis in almost all (16 of 17) who underwent the procedure. The single patient in whom cultures from brain biopsy were negative had *Streptococcus anginosus* bacteremia and was on effective antibiotics before the operation. Six of 42 (14.3%) died within 90 days after presentation.

Infective REBLs vs Neoplastic REBLs

Compared with those with neoplastic REBLs, patients with infective REBLs were younger (55.2 vs 61.6 years old; $P < .001$) and more likely to be male (71.4% vs 51.8%; $P = .02$) (Table 2). Patients with infective REBLs were also more likely to present with fever (38.1% vs 4.0%, $P < .001$). All patients with infective REBLs were symptomatic, compared with about one-fifth (17.3% [43 of 249]) of those with neoplastic REBLs, the lesions being incidental findings on surveillance scans. WBC counts and CRP levels at presentation were significantly higher in patients with infective REBLs than in those with neoplastic REBLs (median WBC count [IQR], 9.9 [7.1–13.8] vs 8.5 [6.5–10.8] $\times 10^3/\mu L$ [$P = .02$]; CRP level, 59.5 [9.4–133.0] vs 12.0 [4.0–90.5] mg/L [$P = .048$]). More than half in each group had multiple REBLs (69.0% vs 60.2%, $P = .31$). Patients with infective REBLs were more likely than those with neoplastic REBLs to have hydrocephalus (28.6% vs 4.8%, respectively; $P < .001$).

PBAs, TBAs, and NBAs

PBAs, TBAs, and NBAs were the 3 most common causes of infective REBLs among the patients in our study. Patients with PBAs, TBAs, or NBAs were similar in age and predominantly male (Table 3). Approximately 40% of those with PBAs and TBAs were immunocompromised, compared with all who had NBAs ($P = .02$). Diabetes mellitus was the leading cause of immunosuppression among patients with PBAs (6 of 20 [30%]), while HIV infection was the leading cause among those with TBAs (4 of 9 [44.4%]). Patients with NBAs were immunosuppressed for various reasons, including hematological cancers (including 1 case in a hematopoietic stem cell transplant recipient), renal transplantation, and high-dose corticosteroid treatment for glomerulonephritis, but none of them had HIV infection.

About one-third of patients in each group had fever at presentation ($P > .99$). The median WBC count (IQR) was highest in patients with PBAs, followed by those with NBAs and those with TBAs, respectively (12.4 [9.1–20.0] vs 10.8 [9.7–15.0] vs 6.9 [6.4–7.2] $\times 10^3/\mu L$; $P = .001$). The median CRP level (IQR) was highest in patients with NBAs, followed by those with PBAs and those with TBAs, respectively (86.6 [22.1–159.0] vs 76.1 [45.0–162.0] vs 8.6 [4.3–51.5] mg/L; $P = .04$).

Abnormal thoracic CT findings were observed in about half (7 of 12 [58.3%]) of the patients with PBAs who underwent thoracic CT, compared with all 8 patients with TBAs and all 6 with NBAs who underwent thoracic CT ($P = .003$). More than half of the patients in each group had multiple REBLs.

Table 3. Characteristics in Patients With Pyogenic, Tuberculous, or *Nocardia* Brain Abscesses

Characteristic	Patients, No. (%)[a]			*P* Value
	PBAs (n = 20)	TBAs (n = 9)	NBAs (n = 6)	
Patient profile				
Age, mean (SD), y	57.4 (15.6)	54.7 (16.0)	59.0 (5.90)	.08
Male sex	13 (65.0)	8 (88.9)	5 (83.3)	.49
Singaporean nationality	20 (100)	7 (77.8)	6 (100)	.09
Immunosuppression (any cause)	7 (35.0)	4 (44.4)	6 (100)	.02
Diabetes mellitus	6 (30.0)	0 (0)	0 (0)	.11
HIV infection	0 (0)	4 (44.4)	0 (0)	.003
End-stage renal failure	1 (5.0)	0 (0)	2[b] (33.3)	.17
Solid organ cancer	1 (5.0)	0 (0)	2 (33.3)	.11
Hematological cancer	0 (0)	0 (0)	3 (50.0)	.003
Solid organ transplant	0 (0)	0 (0)	2 (33.3)	.02
Hematopoietic stem cell transplant	0 (0)	0 (0)	1 (16.7)	.17
Clinical and laboratory features				
Fever as a presenting complaint	7 (35.0)	3 (33.3)	2 (33.3)	>.99
Positive blood culture	11 (55.0)	1 (11.1)	2 (33.3)	.09
WBC count, median (IQR), $\times 10^3/\mu L$	12.4 (9.1–20.0)	6.9 (6.4–7.2)	10.8 (9.7–15.0)	.001
CRP, median (IQR), mg/L	76.1 (45.0–162.0)	8.6 (4.3–51.5)	86.6 (22.1–159.0)	.04
CSF pleocytosis[c]	4[d] (57.1)	3[e] (75.0)	0 (0)	.74
CSF pleocytosis >200 cells/μL[c]	3 (42.3)	0 (0)	0 (0)	.27
Abnormal thoracic CT findings	7[f] (58.3)	8[g] (100)	6 (100)	.03
Neuroimaging features				
Multiple REBLs	11 (55.0)	8 (88.9)	4 (66.7)	.26
Meningeal enhancement	9[h] (47.4)	4 (44.4)	0[i] (0)	.47
Hydrocephalus	8 (40.0)	2 (22.2)	0 (0)	.17
≥1 Lesion >2 cm	13 (65.0)	2 (22.2)	3 (50.0)	.11
DWI hyperintensity	18[j] (100)	5 (55.6)	6 (100)	.003
Hypointense T2 borders in the form of a rim	12[j] (66.7)	1 (11.1)	2 (33.3)	.03
Hypointense T2 borders in the form of an arc	4[j] (22.2)	4 (44.4)	1 (16.7)	.50
Interventions				
LP or EVD insertion	7 (35.0)	4 (44.4)	1 (16.7)	.71
Stereotactic brain biopsy or drainage of abscess	11 (55.0)	2 (22.2)	2 (33.3)	.18
Any brain surgery (including EVD insertion)	12 (60.0)	3 (33.3)	2 (33.3)	.57
Microbiological diagnosis				
Established from blood cultures	11 (55.0)	1 (11.1)	2 (33.3)	.09
Established from respiratory specimens (eg, sputum, lung tissue, or bronchoalveolar fluid)	0 (0)	4 (44.4)	4 (66.7)	<.001
Established from CSF obtained through LP or EVD[c]	1 (14.3)	3 (75.0)	0 (0)	.06
Established from brain tissue or pus[c]	10 (90.9)	2 (100)	2 (100)	>.99
Outcome				
Death within 90 d	5 (25.0)	0 (0)	1 (16.7)	.21

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; DWI, diffusion-weighted imaging; EVD, external ventricular drainage; HIV, human immunodeficiency virus; IQR, interquartile range; LP, lumbar puncture; NBAs, *Nocardia* brain abscesses; PBAs, pyogenic brain abscesses; REBLs, ring-enhancing brain lesions; TBAs, tuberculous brain abscesses; WBC, white blood cell.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]Both patients with end-stage renal failure had undergone renal transplant.

[c]Denominators represent the number of patients who underwent the procedure.

[d]All are predominantly neutrophilic.

[e]All are predominantly lymphocytic.

[f]Thoracic CT was performed in only 12 of 20 patients with PBAs.

[g]Thoracic CT was performed in only 8 of 9 patients with TBAs.

[h]Brain contrast-enhanced CT/magnetic resonance (MR) imaging was performed in only 19 of 20 patients with PBAs.

[i]Brain contrast-enhanced CT/MR imaging was performed in only 3 of 6 patients with NBAs.

[j]Brain MR imaging was performed in only 18 of 20 patients with PBAs.

Neuroimaging features of meningeal enhancement and hydrocephalus were more commonly observed in patients with PBAs and TBAs than in those with NBAs, but the differences were not statistically significant.

All patients with PBAs (18 of 18 [100%]) or NBAs (6 of 6 [100%]) who underwent brain MR imaging had diffusion-weighted imaging (DWI)–hyperintense lesions, compared with only about half (5 of 9 [55.6%]) of those with TBAs ($P = .003$). Hypointense borders on T2-weighted images were present in the form of a rim (as opposed to no hypointense borders or hypointense borders in the form of an arc) in two-thirds of patients with PBAs (12 of 18 [66.7%]), compared with fewer than half of those with TBAs (1 of 9 [11.1%]) or NBAs (2 of 6 [33.3%]) ($P = .03$).

Identification of bacteremia in blood cultures yielded the microbiological diagnosis in more than half of the patients (11 of 20 [55.0%]) with PBAs but only in a minority of those with TBAs (1 of 9 [11.1%]) or NBAs (2 of 6 [33.3%]). Microbiological investigations performed in respiratory specimens did not lead to the diagnosis in patients with PBAs but established the diagnosis in 4 patients (44.4%) with TBAs and 4 (66.7%) with NBAs.

Beyond blood cultures and respiratory specimens, diagnostic evaluation was individualized; not all patients underwent the same invasive procedures. CSF was sampled via LP or EVD in 7 of 20 patients with PBAs (35.0%), 4 of 9 with TBAs (44.4%) and 1 of 6 with NBAs (16.7%). CSF pleocytosis was present in more than half of those with PBAs (4 of 7 [57.1%]) or TBAs (3 of 4 [75.0%]) but was absent in the single patient with NBA who underwent LP ($P = .74$). CSF pleocytosis, when present, was predominantly neutrophilic in all patients with PBAs, while it was predominantly lymphocytic in all patients with TBAs. CSF pleocytosis of >200 cells/μL was observed only in patients with PBAs (3 of 7 [42.3%]) and not in those with TBAs. CSF investigations were less likely to establish the microbiological diagnosis in patients with PBAs (1 of 7 [14.3%]) than in those with TBAs (3 of 4 [75.0%]) ($P = .06$).

More than half (11 of 20 [55.0%]) of patients with PBAs underwent stereotactic brain biopsy or drainage of the abscess. In comparison, fewer than half of the those with TBAs (2 of 9 [22.2%]) or NBAs (2 of 6 [33.3%]) underwent brain biopsy or drainage of the abscess ($P = .18$). Investigations performed on brain tissue or pus yielded the microbiological diagnosis in almost all patients with PBAs (10 of 11 [91.0%]), all with TBAs (2 of 2 [100%]), and all with NBAs (2 of 2 [100%]).

Five patients (25.0%) with PBAs died within 90 days after presentation. Of these, 3 had monomicrobial infections (2 due to *S aureus* and 1 due to *K pneumoniae*) and 2 had polymicrobial infections (1 due to *Weisella viridescens* and *Fusobacterium* species and 1 due to *S anginosus* and *Parvimonas micra*). Three of the deaths could be attributed to the brain abscesses and/or the infective process; 2 patients with *S aureus* infection died of intracranial hemorrhage, while the patient with the *W viridescens* and *Fusobacterium* infection died of new ischemic strokes 4 days after brain surgery. One patient with NBA died within 90 days after presentation. That death was secondary to a nosocomial infection on a background of chronic lymphocytic leukemia. All patients with TBAs survived beyond 90 days. The 90-day mortality rates did not differ significantly between the 3 groups.

DISCUSSION

A prompt diagnosis is key to good clinical outcomes in REBLs, but securing the correct diagnosis can be challenging due to nonspecific presentations, diverse causes, and limitations of standard diagnostic modalities. While no single clinicodemographic or radiological feature is pathognomonic, our study, the first to compare both clinicodemographic and radiological features of infective REBLs, has provided some important diagnostic clues that could aid in the differentiation between infection and neoplasm and between PBAs, TBAs, and NBAs. Our findings also demonstrate the role and yield of the different diagnostic modalities, especially LP and brain biopsy, as well as their pitfalls.

Differentiating Between Infection and Neoplasm

Differentiating between infection and neoplasm is the first step in the evaluation of REBLs, but making this distinction is not straightforward. By comparing patients with infective versus and neoplastic REBLs, we have made some noteworthy observations.

The incidence of neoplastic REBLs was 6 times that of infective REBLs in our study. Metastases, which make up >80% of neoplastic REBLs, far outnumber primary brain tumors. A Mayo clinic study on REBLs demonstrated a similar epidemiology [7]; in their cohort, neoplasms were almost 9 times more common than bacterial abscesses. Accordingly, when the cause is not evident, extracranial imaging such as thoracic, abdominal, and pelvic CT could be useful in identifying undiagnosed primary tumors.

Although fever is classically associated with infection, about two-thirds of patients with infective REBLs were afebrile, making fever an unreliable marker. About one-third of all patients with infective REBLs were bacteremic. Among those with PBAs, about half were bacteremic. As blood cultures offer the chance to clinch the microbiological diagnosis noninvasively and with significant yield, they should be performed whenever infective REBLs are clinically suspected, even when fever is absent.

WBC counts and CRP levels were significantly higher in patients with infective REBLs, but one cannot reliably depend on the level of these inflammatory markers to distinguish between infection and neoplasm due to the wide IQRs with significant overlap. The wide range in values may be due to the inclusion of various causes under the infective and neoplastic categories, each eliciting a different degree of host inflammatory

response. In addition, confounders such as underlying disease states, comorbid conditions, and concurrent pharmacotherapy (eg, chemotherapy, corticosteroids, and antibiotics) can affect the levels of these inflammatory markers.

Role of Brain Biopsy

Brain biopsy is the reference standard for REBL diagnosis. However, the risks of brain biopsy may be high due to lesion location or patient factors. Not uncommonly, clinicians encounter the dilemma of having to decide between attempting LP, hoping that the infectious agent could be identified within the CSF, versus proceeding with the comparatively higher-risk brain biopsy. Attempting LP and waiting for the outcome of CSF investigations risk delaying the diagnosis and clinical deterioration in the interim. In our study, a microbiological diagnosis was established in fewer than half of patients who had CSF sampled, either from LP or EVD, although the sensitivity of CSF studies differs between the infective causes. This low sensitivity of CSF microbiological testing for brain abscesses mirrors findings in other studies [4, 8]. In brain abscesses, the infection may be limited to the brain parenchyma. Predictably, CSF testing is insensitive in identifying the causative infectious agent. Furthermore, LP carries the risk of brain herniation, especially when there is high intracranial pressure [9].

The 6 patients in whom CSF successfully identified an infectious agent included 3 with tuberculosis and 1 each with *K pneumoniae* infection, toxoplasmosis, and cryptococcosis. Apart from *K pneumoniae* infection, these infections tend to occur in the immunocompromised and may manifest concurrently as meningitis and brain abscesses. Despite its limitations, LP may play a role in the immunocompromised population. In contrast to LP, brain biopsy was highly efficacious and yielded the microbiological diagnosis in all but 1 patient who underwent stereotactic brain biopsy or drainage of abscess. Hence, it should be performed expeditiously, especially when less invasive methods prove inconclusive and/or response to empirical treatment is poor. Apart from obtaining clinical specimens for microbiological testing, drainage of the abscess helps with source control by decreasing the intracavitary bacterial load [10], especially when abscesses are large and culture-directed antimicrobials are limited by poor CNS penetration.

Differentiating Between PBAs, TBAs, and NBAs

The most challenging cases are those without a diagnosis and in which brain biopsy cannot be safely performed. Diagnostic clues can heighten clinical suspicion for a specific etiology and prompt empirical treatment. By comparing the 3 most prevalent infective subgroups at our center, PBAs, TBAs, and NBAs, we have identified some diagnostic clues that may aid in the differentiation between these categories.

Determining the net state of immunosuppression in the patient is important in narrowing down the list of differential diagnoses. Notably, NBAs were seen exclusively in patients who were profoundly immunosuppressed. While nocardiosis has been reported among people with HIV [11], none of the patients with NBAs in our cohort had HIV, suggesting that the nocardiosis remains uncommon as an opportunistic infection in this population. Conversely, fewer than half of those with PBAs and TBAs were immunosuppressed. While similar proportions of the patients with PBAs and TBAs were immunosuppressed, the underlying causes of immunosuppression were different—diabetes mellitus was associated with PBAs, while HIV infection was associated with TBAs. These risk factor-disease associations were similarly demonstrated in other studies [12, 13].

Notably, *K pneumoniae* was the most common cause of PBA in our cohort, in contrast to European studies in which *Streptococcus* species were the predominant causes [8, 14]. The hypervirulent serotypes K1/K2 *K pneumoniae,* prevalent throughout Asia and associated with the invasive liver abscess syndrome, was likely responsible [15, 16]. Not surprisingly, diabetes mellitus was a risk factor in *K pneumoniae* infection [17, 18]. Tuberculosis was the predominant cause of REBLs among people with HIV in our study, outnumbering classic causes such as toxoplasmosis and CNS lymphoma [19]. In Singapore, tuberculosis remains endemic, and the incidence of tuberculosis remains at >1000 cases a year [20]. This highlights the importance of correlating local epidemiology with the differential diagnoses.

WBC counts and CRP levels were not useful for differentiating between PBAs, TBAs, and NBAs. While patients with PBAs and NBAs tended to have higher inflammatory markers than those with TBAs, wide IQRs, due to confounders such as underlying disease states and concurrent pharmacotherapy, render these markers nonspecific and unreliable for etiological differentiation.

Thoracic CT is a high-yield investigation, especially in the immunocompromised. The likelihood of an abnormal scan was high among our patients with TBAs and NBAs, diseases that may present with a lung-brain syndrome. An abnormal thoracic CT scan could provide diagnostic clues when certain radiological features are present (eg, miliary nodules) and offer a more accessible site for tissue sampling. Investigations performed on respiratory specimens yielded the microbiological diagnosis in about half of patients with TBAs and two-thirds of those with NBAs, obviating the need for a brain biopsy and underscoring the value of pursuing bronchoscopy or transthoracic needle biopsy for suspicious pulmonary lesions in these patients.

The MR neuroimaging features of PBAs may differ from those of TBAs and NBAs. Schwartz et al [7] reported that the MR features, DWI hyperintensity, and T2 hypointense borders in the form of a rim favored PBAs over neoplasms. Lesional DWI hyperintensity or a reduced apparent diffusion coefficient

[1, 7] were observed in all patients with PBAs and NBAs but just about half of those with TBAs. T2 hypointense borders in the form of a rim [7] were seen in two-thirds of the patients with PBAs but fewer than half of those with TBAs or NBAs. Our findings caution against the extrapolation of these MR features to all infective causes of REBLs, particularly in immunocompromised hosts who are susceptible to opportunistic CNS infections.

Strengths and Limitations

The main strength of the study was the high-quality clinical data that were obtained through close multidisciplinary collaboration between infectious diseases and neuroradiology personnel, who meticulously reviewed the electronic medical records and neuroimaging to ensure that only patients whose diagnoses were certain were included in our study. While there have been published studies comparing the MR appearances for different causes of abscesses [21, 22], ours is the first study comparing both clinicodemographic and radiological features of various infective causes of REBLs. Another strength is our study population, of which a significant proportion were immunocompromised and thus susceptible to opportunistic infections. Consequently, we were able to analyze uncommon causes of infective REBLs, such as TBAs and NBAs.

Our study did have some limitations. The relatively small sample size of patients with infective REBLs may prevent us from detecting differences between the various causes of REBLs. Our cohort included very few cases of cryptococcosis, toxoplasmosis, aspergillosis, and neurocysticercosis. The clinical presentations of these conditions tend to differ from those of PBAs, TBAs, and NBAs, but because of the small number of cases, we were unable to include these infective etiologies in the analysis (Supplementary Table 1). Due to the retrospective nature of our study, the findings are subject to confounding, such as variation in clinical practice between different physicians. Missing data (eg, absent laboratory values) may lead to bias in data interpretation. To mitigate these limitations, further recruitment to achieve a larger sample and a prospective arm would be helpful. As ours was a single-center study with a study population that is predominantly Singaporean, its findings may not be generalizable to overseas centers.

Conclusions

Our study has highlighted the challenges that clinicians presently face in the evaluation of REBLs. An awareness of the distinguishing clinicodemographic and radiological features between the various etiologies and their pitfalls could improve diagnostic strategies, facilitate timely diagnosis, and potentially lead to improved patient outcomes. For now, an individualized approach integrating sound clinical judgment with various diagnostic modalities remains the best course of action. As long as brain biopsy remains prohibitive for some patients, there is a need for improved, noninvasive diagnostic tools. MR imaging–based radiomics and deep-learning models have shown potential in predicting the grade and molecular classification of brain tumors [23, 24] and differentiating brain abscess from brain metastases [25] and necrotic glioblastomas [26]. A model incorporating both clinicodemographic features and multisequence MR imaging data may offer a solution.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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