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Persistent Neutrophilic Meningitis

REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE

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Introduction

Neutrophilic (purulent) meningitis is characterized by hypoglycorrhachia, an elevated protein concentration, and a predominance of polymorphonuclear leukocytes in the cerebrospinal fluid (CSF) (86, 158). Bacteria are the major cause of this syndrome (86, 158) although a plethora of other uncommon infectious and noninfectious etiologies have been described (86, 158). Among the bacterial pathogens producing neutrophilic meningitis, *Hemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis* and Group B streptococci account for the vast majority of cases (86, 111, 158). The initial management of neutrophilic meningitis usually consists of antimicrobial therapy directed against one or more of these common pathogens (86, 111, 158). Subsequent patient management may be modified by several factors, including clinical response to initial therapy, CSF culture results and results of additional CSF analyses.

Response to appropriately treated neutrophilic (predominantly bacterial) meningitis is usually prompt with improvement in clinical status often apparent within 24 to 48 hours and resolution of most signs and symptoms occurring by 3 to 5 days (86, 150, 158). In cases exhibiting clinical improvement, repeat CSF analysis is generally not indicated (2, 159). However, if clinical progress seems unsatisfactory, if fever persists or recurs, or if the etiology of meningeal inflammation remains uncertain, a repeat CSF examination should be performed (158, 159). A favorable CSF response to antimicrobial therapy is manifested by a decreasing leukocyte count, a shift in the leukocyte differential to lymphocytic predominance, and a gradual return of glucose and protein levels toward normal (35, 86, 150, 158). A lack of improvement in CSF parameters suggests either that therapy has been inadequate (suboptimal drug activity, dosage or CSF penetration; resistant organism) or that a neurologic complication has developed (86, 158). If this lack of improvement in CSF parameters is manifested as a persisting neutrophilic CSF profile, especially if bacterial cultures of CSF remain negative, then the clinician is faced with an uncommon and frequently puzzling clinical problem. Among defined causes of the "aseptic meningitis syndrome" (111), etiologies which would result in persistent CSF neutrophilia, especially for more than 1 week, are distinctly unusual. "Chronic" cases of neutrophilic meningitis have been reported rarely and the entity of persistent neutrophilic meningitis is not recognized nor discussed in reviews of "chronic" meningitis (51, 52). In this report, we describe four patients with persistent neutrophilic meningitis and review potential diagnostic considerations for this syndrome.

Methods

As described in this paper, patients classified as having "persistent neutrophilic meningitis" exhibited all of the following clinical features: 1) symptoms and signs suggesting meningitis (headache, altered sensorium, fever, meningismus); 2) initial CSF analysis revealing ≥50% polymorphonuclear leukocytes (neutrophils) on differential count with concurrent elevated protein and depressed glucose concentrations; 3) therapy with an accepted parenteral antimicrobial regimen, appropriate for the presumed cause of the meningitis based on clinical presentation and initial CSF analysis; 4) negative smears and cultures of the initial CSF specimen for bacteria; and 5) repeat CSF analysis ≥1 week after the initial study revealing persistent neutrophilic pleocytosis (≥ 50% neutrophils), increased protein concentration, and hypoglycorrhachia.

In accordance with this case definition, four patients hospitalized at the North Carolina Memorial Hospital (NCMH) in recent years were identified as having persistent neutrophilic

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meningitis. Cases 1 and 4 have been described briefly in earlier reports (79, 164).

Case Reports

Case 1

A 23-year-old man was admitted to NCMH for chemotherapy of a myeloproliferative disorder characterized by refractory anemia with excess blasts. Admission chest x-ray was normal. When vincristine and prednisone failed to elicit a clinical response, the chemotherapeutic regimen was altered to high-dose cytosine arabinoside and L-asparaginase, after which pancytopenia rapidly ensued. On the 32nd hospital day, fever developed and empiric therapy with carbenicillin and tobramycin was begun. The patient's fever subsequently defervesced although cultures were negative. Six days later, fever redeveloped and the patient complained of headache. A lumbar puncture was normal, sinus films were negative, and a computed tomogram (CT) of the head was normal. Cefazolin was added but fever persisted and a chest x-ray showed new nodular upper lobe densities. Following percutaneous needle biopsy of a right upper lobe nodule, empiric therapy with amphotericin B was instituted. Examination of the needle biopsy specimen was negative by Gram stain, KOH smear, India ink smear, and fluorochrome stain; bacterial and fungal cultures were negative; cytology revealed a few "atypical cells" which were non-diagnostic.

Over the next week, the patient remained intermittently febrile. Profound neutropenia persisted and additional cavitary nodules appeared on chest x-ray. The patient's headache worsened but his neurologic examination remained unchanged.

By day 57, the white blood cell count had gradually risen to 1100/mm^3 with 500 neutrophils/mm^3 but fever persisted, as did the nodular pulmonary infiltrates. Carbenicillin and cefazolin were discontinued. The following day, meningismus was noted and the patient appeared more lethargic. Lumbar puncture revealed a neutrophilic profile (Table 1) but microscopic examination of the fluid was negative. A regimen of ampicillin and oxacillin was begun with continuation of tobramycin, trimethoprim-sulfamethoxazole and amphotericin B. CT study of the head and sinuses was negative, as was an otorhinologic exam. Bacterial cultures and cryptococcal antigen of CSF were negative. A repeat lumbar puncture on day 63 revealed persistent CSF abnormalities but examination of the fluid for bacterial and fungal organisms was again negative. The pulmonary infiltrates remained unchanged and on the 65th hospital day, open lung biopsy was performed. Histologic examination of the tissue revealed an extensive necrotizing pneumonitis with hyphae consistent with *Aspergillus*; cultures subsequently grew *Aspergillus terreus*. Although CSF cultures remained negative, the clinical impression was disseminated aspergillosis with central nervous system (CNS) involvement. The latter diagnosis was subsequently confirmed by detection of aspergillus antigen in CSF specimens using a radioimmunoassay (166, 167). Amphotericin B was continued at 1 mg/kg/d and 5-flucytosine and rifampin were added. However, the patient's neurologic status continued to deteriorate and he died with profound neurologic dysfunction and respiratory failure.

On postmortem examination, bilateral cavitating bronchopneumonia was present. Microscopic examination of lung tissue revealed extensive necrotizing pneumonitis; special stains for fungi demonstrated branching hyphae characteristic of *A. terreus* throughout all lobes, with vascular invasion apparent in the right upper lobe. Examination of the brain revealed tonsillar herniation and a generalized inflammatory exudate; multiple infarcts were noted, as was an abscess in the right cerebellar hemisphere. Exudate was seen occluding the 4th ventricle. Microscopically, *Aspergillus* was identified in the leptomeningeal exudate and in areas of necrotizing vasculitis in the pons and basal ganglia. Incidentally noted were abscesses in the liver, thyroid and renal medullae. Although hypoplastic, all specimens of bone marrow were consistent with complete remission of the leukemic process. Postmortem specimens of lung tissue grew *A. terreus*.

Comment: This case clearly demonstrates the diagnostic dilemma posed by persistent neutrophilic meningitis in the compromised host. Despite very broad-spectrum therapy, the patient manifested progressive clinical deterioration. An inferential diagnosis of CNS aspergillosis was ultimately provided by lung biopsy which revealed extensive pulmonary aspergillosis with areas of vascular invasion. The fruitless attempts at direct CNS diagnosis via repetitive studies of CSF emphasize the diagnostic utility of biopsy of extraneural sites of disease. It should be noted, however, that an ante-

TABLE 1. Summary of cerebrospinal fluid (CSF) findings in the reported patients*

Patient	CSF WBC Count (Range, cells/mm^3)	Differential Neutrophil Count (Range, %)	Glucose (Range, mg/dl)	Protein (Range, mg/dl)	Smear†/ Culture‡ Results	Total Duration of CSF Neutrophilia (Days)
Case #1	117–1126	88–99	13–48	54–346	Neg/Neg	14
Case #2	17–1000	61–100	20–54	63–2500	Neg/Neg	209
Case #3	97–570	56–94	28–82	43–176	Neg/Neg	25
Case #4	156–3050	40–90	<25–45	48–1018	Neg/Neg	32

* All reported data from studies performed on cerebrospinal fluid (CSF) obtained via lumbar puncture. WBC = white blood cell; Neg = negative.

† "Smear" refers to all routine microscopic studies performed on CSF to detect organisms (i.e., Gram stain, fluorochrome or Kinyoun stains, potassium hydroxide, India ink).

‡ Routine cultures performed on CSF included aerobic and anaerobic bacterial cultures, cultures for *M. tuberculosis* and fungal cultures. Sheep blood agar and chocolate agar were the media routinely employed for bacterial cultures; cultures were incubated at 35–37°C in 5% CO_2 for 10 to 14 days before being discarded as negative. Cultures for *M. tuberculosis* and fungi were performed using standard techniques (112) and were held for 4–6 weeks.

mortem diagnosis of CNS aspergillosis was accomplished through detection of *Aspergillus* antigen in both lumbar and ventricular CSF. The ready application of antigen detection methodology to CSF in this case suggests that similar techniques may play an important future role in the rapid diagnosis of chronic meningitis due to organisms such as *Aspergillus*, which are difficult to isolate in culture.

Case 2

A 42-year-old tobacco farmer was well until 4 months before his initial NCMH admission, when he developed weight loss, fever, and a productive cough. When chest x-ray revealed a right upper lobe infiltrate, a presumptive diagnosis of tuberculosis was made and therapy with isoniazid and para-aminosalicylic acid was initiated. Two months later, headache and confusion developed. Cranial CT scan revealed only ventricular dilatation; brain scan, skull films, and carotid angiograms were normal. Intermediate strength PPD, *Candida*, and *Histoplasma* skin tests were nonreactive. Chest x-ray revealed interval clearing of the right upper lobe infiltrate. Serial lumbar punctures (data not shown) demonstrated persistent neutrophilic pleocytosis, elevated protein concentrations and hypoglycorrhachia. Stains, bacterial cultures, cytologies and India ink preparations of CSF were uniformly negative.

The patient was transferred to NCMH for evaluation of chronic meningitis. Lumbar puncture again revealed neutrophilic pleocytosis (Table 1) but CSF cultures remained sterile despite special handling, the use of selective media and prolonged incubation. Repeat cranial CT scan was normal. Serological studies for *Blastomyces*, *Histoplasma*, *Coccidioides*, *Aspergillus*, and *Toxoplasma* species were negative. When left mastoid tomograms demonstrated mastoiditis, a simple left mastoidectomy was performed, which revealed only chronically inflammed granulation tissue. Pathologic examination demonstrated foreign body giant cells and thickened fibrotic tissue suggestive of meninges; no organisms were seen.

One week later, chest pain, dyspnea and hypoxemia developed. A review of serial chest x-rays revealed progressive rightward deviation of the trachea. An aortogram demonstrated an aneurysm arising from the aortic arch. The patient underwent exploratory thoracotomy where a presumed mycotic aneurysm was resected. Cultures of the aneurysm grew *Nocardia caviae* and therapy with ampicillin and erythromycin was initiated (the patient was sulfa-allergic).

Over the next 6 months, the patient developed neurologic findings consistent with a subarachnoid block at C5-C6, presumed secondary to chronic arachnoiditis. Repeat aortography suggested recurrence of the aortic aneurysm. A second thoracotomy revealed diffuse inflammatory involvement of the mediastinum which precluded resection of the aneurysm. Postoperatively, clinical deterioration continued, and 2 months later the patient died.

On postmortem examination, a large aneurysm was noted arising from the aorta, with surrounding fibrosis and necrosis of the mediastinum. The meninges were fibrotic and adherent to the surrounding bony structures. The spinal cord had marked thickening of the arachnoid membranes at the cervical and thoracic levels. There was severe hydrocephalus. Microscopic examination of the brain showed patchy lymphocytic leptomeningitis. In one area of the pontine leptomeninges, there was a small area of granulomatous inflammation as well as a dense infiltrate of chronic inflammatory cells and focal necrosis. The spinal cord exhibited chronic fibrosing arachnoiditis. Organisms were not demonstrated by special stains or culture.

Comment: In this case, disseminated nocardiosis with presumed meningeal involvement led to CSF neutrophilic pleocytosis persisting over several months, even after initiation of therapy for nocardiosis. Although definitive diagnosis of CNS nocardiosis was not accomplished, cultural documentation of extraneural nocardial disease certainly supports an inferential diagnosis of CNS nocardiosis and again emphasizes the role of examination of involved extraneural tissues in diagnosis. The patient died with progressive cord destruction shown pathologically to be due to fibrosing arachnoiditis without demonstrable active infection.

Case 3

A 65-year-old white man with chronic bronchitis was well until March 1982, when he developed increasing shortness of breath. After a chest x-ray revealed bilateral nodular pulmonary infiltrates, bronchoscopy was performed. Although stains of the bronchoscopic washings demonstrated branching filamentous gram-positive organisms and cultures grew *Nocardia asteroides*, the patient was treated only with doxycycline, bronchodilators, and prednisone; no specific anti-nocardial therapy was administered. He nevertheless did well until May when fever, chills, and dysuria developed. He was evaluated as an outpatient and treated with cefaclor and doxycycline without improvement. Upon re-admission to his local hospital, it was noted that he was lethargic, with mild meningismus. Repeat chest x-ray revealed resolution of the previously noted nodular densities but a persistent infiltrate was present in the left lower lobe. Treatment with cefamandole and gentamicin was begun. A cranial CT scan was within normal limits. Lumbar puncture revealed WBC 457/mm^3 with 87% neutrophils and 13% lymphocytes, protein 112 mg/dl, and glucose 28 mg/dl. The patient's antimicrobial therapy was then changed to intravenous trimethoprim-sulfamethoxazole, cefotaxime, isoniazid and rifampin and he was transferred to NCMH.

A cranial CT scan and a brain scan were negative. Lumbar puncture again revealed a neutrophilic profile. The patient was initially treated with moxalactam, trimethoprim-sulfamethoxazole, isoniazid, rifampin, and ethambutol. CSF cultures were sterile and CSF antigen screens and microscopic examinations were negative. When repeat lumbar puncture demonstrated improvement in the CSF parameters, the moxalactam was discontinued. The patient remained on trimethoprim-sulfamethoxazole and antituberculous therapy with gradual improvement in his mental status. Lumbar puncture prior to discharge revealed significant improvement in all parameters but chronic therapy with trimethoprim-sulfamethoxazole alone was continued. The patient subsequently received trimethoprim-sulfamethoxazole for an additional four months during which time serial lumbar punctures demonstrated a gradual normalization of all CSF parameters (data not shown). Repeat CT scan was not obtained. Eighteen months after discontinuing therapy, the patient is clinically well without evidence of neurologic disease or abnormalities.

Comment: This patient, chronically immunosuppressed through treatment with oral prednisone, developed culture-proven nocardial pneumonitis which was initially inappropriately treated. His superimposed neurologic syndrome presumably represented disseminated CNS nocardiosis, although cultural proof of that diagnosis was not obtained. Throughout his early course, CSF analysis revealed persistent neutrophilia. Even after appropriate anti-nocardial therapy was initiated, CSF parameters did not exhibit improvement for 2 to 3 weeks and his final lumbar puncture still revealed a minimal neutrophilic pleocytosis.

Case 4

A 2-month-old male infant was admitted to NCMH with a 2-week history of vomiting, diarrhea, and fever. He was afebrile but appeared chronically ill. Left facial paralysis and a proptotic left eye were present. Purulent drainage was noted in the left external auditory canal and in both nostrils. A black necrotic ulcer involving the hard and soft palates and extending into the nasopharynx was present. The neck was supple. Sinus roentgenograms were remarkable only for opacification of the left maxillary sinus. Lumbar puncture revealed hazy CSF with WBC 1300/mm^3, 90% of which were neutrophils. Direct microscopic examination of the CSF was unrevealing. Biopsy of the palatal ulcer was non-diagnostic, demonstrating only granulomatous changes.

Empiric broad-spectrum antibiotic therapy was initiated without clinical improvement. Repeat lumbar puncture revealed decreasing CSF leukocytosis and neutrophilia though the protein and glucose concentrations were unchanged. All CSF cultures remained sterile. On the 9th hospital day, a second biopsy of the palatal ulcer demonstrated the presence of broad nonseptate hyphae consistent with a zygomycete. Therapy with intravenous amphotericin B was initiated, after which the patient demonstrated improvement in his CSF glucose and protein concentrations though CSF neutrophilia persisted. Despite continued vigorous antifungal therapy, the patient exhibited progressive neurologic dysfunction. When repeat lumbar puncture revealed WBC count 3050/mm^3 with 90% neutrophils, intrathecal therapy with amphotericin was initiated but the patient's deterioration continued and he died.

At postmortem examination, the palatal ulcer was demonstrated to communicate with the nasopharynx, the left orbit and the left frontal lobe of the brain through a defect in the cribriform plate. Bilateral frontal lobe abscesses were present. Both abscess cavities, the entire ventricular system, the left orbit and the middle ears were filled with purulent exudate. A severe purulent meningitis and panvasculitis were also present. Broad nonseptate hyphae were demonstrated microscopically in the orbital tissue but not within the central nervous system proper. Special stains revealed clumps of bacteria within the meninges and periventricular cerebral structures, and postmortem CSF cultures grew *Staphylococcus aureus* and *Proteus morganii*.

Comment: In this case, an infant developed rhinocerebral zygomycosis presumably secondary to diarrhea-associated acidosis. Although the clinical presentation was classic, the initial inability to demonstrate organisms on biopsy of the palatal ulcer and the concomitant presence of persistent neutrophilic meningitis led to diagnostic uncertainty. Only after a repeat palatal biopsy demonstrated broad nonseptate hyphae was amphotericin B therapy initiated. Terminally, the patient experienced purulent bacterial meningitis secondary to a nasopharyngeal–CNS communication.

Discussion

The four patients reported herein all had persistent meningitis characterized by neutrophilic cerebrospinal fluid profiles. In all cases, routine bacterial pathogens were excluded as etiologic causes of meningitis on the basis of multiple negative CSF smears and cultures and by the lack of response to appropriate empiric antibacterial therapies. Serial CSF analyses documented the persistence of neutrophilic leukocytosis in the CSF in all patients over extended periods of time. The failure to isolate typical bacterial pathogens from the CSF and the continued survival of the affected patients in the face of a persistent neutrophilic CSF profile identified these patients as having an unusual "chronic" meningitis syndrome.

The syndrome of chronic meningitis has been well delineated in recent reviews (51, 52). However, with few exceptions, the majority of patients described in those reviews have exhibited lymphocytic CSF profiles (51, 52). Neutrophil predominance and persistence in the CSF serves to identify a special subset of patients who have not been well characterized as to etiology. Swartz recently noted that chronic meningitis may, on rare occasions, be characterized by a neutrophilic CSF pleocytosis and suggested that *Actinomyces* and *Nocardia* were potential etiologic pathogens but no references or supportive data were provided (158). The cases described in this report and our review of available literature have led us to identify a number of well-documented etiologies for the syndrome of persistent neutrophilic meningitis (Tables 2 and 3). Although a comprehensive literature review was attempted, incomplete information in case reports and lack of serial or follow-up CSF data in many instances suggest that the causes shown in Table 3 should be considered representative rather than inclusive.

Saprophytic bacterial pathogens

Several saprophytic intracellular bacteria have clearly been shown to produce meningitis characterized by persistent CSF neutrophilia. These agents may cause infections in immunologically intact hosts as well as in those who are immuno-

TABLE 2. Cases of persistent neutrophilic meningitis: literature review

Etiologic Category	Age (years)/ Sex	Underlying Disease	Duration of Symptoms Before LP	CSF Studies: WBC Count (Range, cells/ mm^3)	CSF Studies: Neutrophils (Range, %)	CSF Studies: Glucose (Range, mg/dl)	CSF Studies: Protein (Range, mg/dl)	CSF Studies: Stains/ Smears	CSF Studies: Cultures	CSF Studies: Duration of CSF Neutrophilia	Mode of Diagnosis	References
INFECTIOUS												
Saprophytic												
Bacteria												
1. *Nocardia asteroides*	39/M	None	6 d	200–2400	60–98	36–45	137–960	NS	+	8 wks	Culture of large volume of CSF	138
2. *Nocardia asteroides*	28/F	None	1 d	1300–7000	83	0–36	+	–	+	~2 wks	Culture of CSF	87
3. *Nocardia asteroides*	32/M	None	5 d	63–4000	<50–100	35	80–2200	–	+	3 mos	Culture of CSF	71
4. *Actinomyces bovis*	22/F	None	4 d	200–619	50–95	50	130–160	–	–	6 wks	Culture of brain abscess	13
5. *Arachnia propionica*	13/M	None	? yrs	1500–4345	>50–100	11–17	174–189	–	–	>2 mos	Culture of epidural abscess	3, 52
6. *Brucella suis*	22/M	None	3 mos	>300	60	NS	NS	+	+	Wks	Culture of CSF	60
Mycobacteria												
7. *Mycobacterium tuberculosis*	17/F	NS	NS	833–1740	76–80	27–40	75–228	–	–	8 days	Autopsy	113
Fungi												
8. *Blastomyces dermatitidis*	43/M	None	1 yr	190–840	89–100	25	80–140	–	–	Wks	Meningeal biopsy	72
9. *Blastomyces dermatitidis*	53/M	None	>1 mo	112–388	70–100	23–29	144–175	+	–	~3 wks	Ventriculostomy	98
10. *Histoplasma capsulatum*	59/M	None	2 mos	100–200	90–95	35–70	29–126	–	–	>2 wks	Autopsy	69
11. *Coccidioides immitis*	55/M	None	3 wks	43–165	100	47	80	–	–	12 d	Culture of urine and sputum	136
12. *Candida albicans*	62/M	None	Days	66–1900	>50	NS	72	+	+	>1 mo	Culture of CSF	61
13. *Candida albicans*	66/F	Chronic myelogenous leukemia	~1 wk	10–347	0–96	37–52	19–114	–	+	~10 wks	Culture of CSF	42
14. *Candida albicans*	<1/M	None	? wks	~10–650	20–100	10–30	30–245	–	+	3–4 wks	Culture of CSF	97
15. *Aspergillus oryzae*	34/F	IV drug abuse	Wks	68–4670	0–95	16–65	44–175	+	+	3 mos	Culture of CSF	76
16. *Aspergillus* species	36/M	IV drug abuse	Days	0–1292	27–93	29–62	10–216	–	–	? wks	Autopsy	120
17. *Pseudoallescheria boydii*	46/F	None	Mos	33–4574	66–98	35	98–3318	NS	+	~4 mos	Culture of CSF	9
18. Zygomycete	61/M	None	1 wk	34–824	0–95	70–162	11–74	–	–	2 mos	Meningeal and clivus biopsy	89
19. *Cladosporium trichoides*	17/M	None	5 mos	136–1150	41–97	22–48	117–3000	–	–	~5 mos	Autopsy	19, 52

TABLE 2. *(continued)*

Etiologic Category	Age (years)/ Sex	Underlying Disease	Duration of Symptoms Before LP	CSF Studies						Mode of Diagnosis	References
				WBC Count (Range, cells/ mm^3)	Neutrophils (Range, %)	Glucose (Range, mg/dl)	Protein (Range, mg/dl)	Stains/ Smears	Cultures	Duration of CSF Neutrophilia	
NONINFECTIOUS											
20. Epidermoid cyst	1/F	Hereditary spherocytosis	11 d	100–1120	60–90	48–62	<40–54	–	–	<2 wks	Autopsy	145
21. Intrathecal gentamicin	30/F	Aqueductal stenosis	~4 d	11–1911	75–100	31–41	75–360	–	–	~2 wks	Clinical observation	28
22. ? Mollaret's	7/F	None	~1 wk	1700–4000	80–90	NS	NS	NS	–	~3 wks	Clinical exclusion	160
23. Systemic lupus erythematosus (SLE)	61/M	SLE	Days	0–2817	0–98	42–115	42–212	–	–	2 mos	Skin biopsy	62

Abbreviations: LP = lumbar puncture; WBC = white blood cell; CSF = cerebrospinal fluid; M = male; F = female; d = day; wks = weeks; mos = months; yr = year; NS = not stated; IV = intravenous; – = negative; + = positive.

TABLE 3. Documented etiologies of persistent neutrophilic meningitis*

	Infectious	Noninfectious
Common	Actinomycosis Nocardiosis Candidiasis Aspergillosis Zygomycosis Dematiomycosis	Chemical meningitis Systemic lupus erythematosus
Uncommon but reported	Brucellosis Tuberculosis Blastomycosis Histoplasmosis Coccidioidomycosis Pseudoallescheriasis	? Mollaret's

* As defined in Methods. Common etiologies are those for which there are several case reports or other corroborative sources; uncommon etiologies are those for which there are usually only isolated case reports.

compromised. Among agents warranting etiologic consideration, *Nocardia*, *Actinomyces*, and *Brucella* have been most clearly associated with the syndrome of persistent neutrophilic meningitis (Table 2).

Central nervous system nocardiosis occurs in 15 to 40% of cases with nocardial infection (15, 130, 138). Although brain abscess is the most characteristic neurologic lesion, meningitis may also occur (58, 102, 138). Cerebrospinal fluid findings in CNS nocardiosis are largely nondiagnostic (102). In reported cases of nocardial meningitis, with or without brain abscess, either lymphocytes (86, 153) or neutrophils (21, 39, 58, 71, 87, 138, 173) may predominate in the CSF; elevated CSF protein concentrations and hypoglycorrhachia are usually present (21, 39, 58, 71, 87, 96, 138, 153, 173). Several case reports of nocardial meningitis (71, 87, 138) clearly document the occurrence of persistent CSF neutrophilic pleocytosis, as seen in our Cases 2 and 3.

Actinomycosis of the central nervous system has become rare in the antibiotic era (27, 103). The usual manifestation of CNS disease is brain abscess (24, 27, 64, 103), though isolated cases of either meningitis alone (24, 46, 52, 64) or meningitis occurring in conjunction with brain abscess (13, 24, 64) have been described. The typical CSF findings in cases of meningitis, either with or without brain abscess, are those of a purulent or neutrophilic process (13, 24, 64). Several authors have emphasized that extreme CSF purulence with fluid resembling pure pus is characteristic of actinomycotic meningitis (13, 24, 46, 52, 64). Because of the relatively indolent nature of the pathogen, subacute or chronic presentations of CNS disease can occur (3, 13, 24, 46, 81), and persistent neutrophilic pleocytosis has been documented (3, 13). Since cultures of CSF are rarely if ever positive for the organism

(64), persistent neutrophilic meningitis of unclear etiology may be the resultant clinical picture (158).

Protean neurologic manifestations have been described in association with brucellosis (1, 100, 151). Although relatively unusual, subacute neurobrucellosis with a persistent neutrophilic CSF profile has been described (60, 124).

Mycobacteria

Meningitis due to *Mycobacterium tuberculosis* typically produces a CSF profile characterized by lymphocytic pleocytosis, elevated protein concentrations and hypoglycorrhachia (51, 86, 91, 111, 113, 155, 158). However, neutrophilic pleocytosis is not infrequently seen, especially in the early phases of disease (12, 86, 91, 94, 111, 158). If serial CSF analysis is undertaken in patients with early neutrophilic tuberculous meningitis, conversion to a lymphocytic pleocytosis usually ensues within 7 days (105, 113). Nevertheless, occasional reports have documented the persistence of a neutrophilic pleocytosis for longer than one to two weeks (113, 119). In fact, some authors have emphasized that marked variability in the CSF cell count with transient increases in CSF neutrophils during the early stages of disease should suggest the diagnosis of tuberculous meningitis (40, 52, 101).

Fungi

The clinical presentations of fungal meningitis are diverse (162). Although the "typical" CSF profile is a lymphocytic pleocytosis with low or normal glucose levels and an elevated protein concentration (86, 158, 162), predominant neutrophilic CSF responses occasionally occur and are said to be "characteristic" of certain types of fungal CNS infections (162). As exemplified by our Cases 1 and 4, at least two fungal pathogens—*Aspergillus* and the zygomycetes—may produce persistent neutrophilic meningitis. In addition, available literature suggests that *Candida*, *Pseudoallescheria* and the dematiaceous fungi, as well as primary systemic mycoses such as *Blastomyces*, *Histoplasma*, and *Coccidioides*, are also capable of producing this syndrome.

Central nervous system aspergillosis usually occurs in the setting of disseminated infection in the immunocompromised host (5, 58, 152, 172). Single or multiple brain abscesses, meningitis, meningoencephalitis, single granulomas and cerebral infarction are manifestations of CNS disease that have been described (17, 121, 152). Onset of these various CNS syndromes may be acute, subacute or chronic (84, 152). In patients with meningitis, examination of the CSF is often not diagnostically helpful (5), as the findings are quite variable and cultures are usually negative (84, 117, 121, 152, 172). Pleocytosis, if present, is usually limited, with a cell count less than 600/mm^3 (58). Although many authors emphasize that the pleocytosis may be either lymphocytic or neutrophilic (5, 172), others suggest that neutrophils usually predominate (58, 162). Occasional patients (76, 84, 92, 120, 156, 172), including our Case 1, exhibit a neutrophilic CSF formula that may persist for greater than 1 week (Case 1; references 76, 120).

Central nervous system zygomycosis typically occurs in association with rhinocerebral disease or disseminated infection in the compromised host (48, 114, 115). In rhinocerebral disease, findings referable to the nasopharynx, sinuses and/or orbit are usually prominent and lead to a consideration of a zygomycete as the etiologic agent (48, 114, 115). However, as was seen with our Case 4, definitive diagnosis can be difficult and is contingent upon demonstration of the organism in scrapings or biopsy specimens. Examination of the CSF in patients with CNS involvement generally reveals nonspecific findings (48), which may include low-grade pleocytosis with equal numbers of neutrophils and lymphocytes and slight protein elevations (48, 58, 114, 115). However, a number of authors have emphasized that the predominant cellular response in CNS zygomycosis is neutrophilic (57, 67). That suggestion is supported by the recent observations of Meyers et al (118), who found a neutrophilic predominance in four of five patients with rhinocerebral zygomycosis who exhibited CSF pleocytosis. In disseminated zygomycosis with CNS involvement, focal parenchymal disease in the form of infarcts or abscesses usually results (33, 114–116); the meninges may or may not be involved (33). Examination of CSF in such cases is generally not diagnostically helpful (114, 116). A very low-grade pleocytosis, typically lymphocytic, is usually seen (116), although at least one reported patient exhibited 50% neutrophils on differential count (116). Although untreated zygomycotic disease of any type is usually rapidly fatal, occasional indolent or chronic cases do occur (114, 132). Few data are available in such cases on the persistence or evolution of various CSF abnormalities with time. However, Jones et al recently reported a patient with focal intracranial zygomycosis who clinically presented with chronic meningitis (89). Although initial CSF analyses revealed a lymphocytic pleocytosis, the patient subsequently developed a neutrophil predominance, which persisted for over 1 month.

Although previously considered to be relatively rare (6, 58), candidiasis is now recognized as the most common mycotic infection involving the central nervous system (131). CNS candidiasis may be

manifest as either diffuse parenchymal microabscesses or as a subacute or chronic meningitis (49). Meningitis may arise *de novo* or as a complication of disseminated candidal infection (49). Virtually all patients with meningitis exhibit a CSF pleocytosis, the average cell count being 600/mm^3 (14, 49, 58). Either lymphocytes or neutrophils may predominate (14, 49, 58). In their review of 28 cases of candidal meningitis, Bayer et al (14) found a neutrophilic pleocytosis in 52%. Black, in his review of cerebral candidiasis (23), stated that the CSF findings were similar to those of pyogenic bacterial meningitis, including the predominance of neutrophils. Thus, it would appear that a purulent/neutrophilic CSF profile is common in candidal meningitis. The duration of persistence of the neutrophilic pleocytosis has not been well defined, although at least three reported cases have exhibited neutrophilic predominance on serial lumbar punctures for periods exceeding two weeks (42, 61, 97).

Pseudoallescheria boydii produces a variety of infectious syndromes, including meningitis and brain abscess (18, 170). In cases with meningitis, either with or without concurrent brain abscess, CSF pleocytosis is often present and may be either lymphocytic (16) or, more typically, neutrophilic (9, 53, 170). In one report (9), neutrophilic pleocytosis persisted over a 4 month period.

The dematiaceous fungi are a rare but well-described cause of central nervous system infection in man (19, 58). Brain abscess with focal neurologic signs is the usual clinical presentation, although focal and diffuse meningitis has been reported as well (19). In their review of cerebral dematiomycosis, Bennett et al (19) characterized 10 patients with meningitis and noted that neutrophilic CSF pleocytosis was a frequent finding. They reported in detail on a patient with chronic meningitis caused by *Cladosporium trichoides* who exhibited persistent neutrophilic CSF pleocytosis over a 5 month period (19, 52).

Central nervous system involvement with the systemic mycoses ranges from 3 to 10% with blastomycosis (58, 59, 72) to up to 50% with histoplasmosis (38, 58, 74) and coccidioidomycosis (25, 50). Neurologic syndromes may be acute or chronic and include meningitis, focal cerebritis and intracranial or spinal mass lesions (50, 58, 72, 74). Either neutrophilic or lymphocytic pleocytosis may be seen on CSF analysis, with the latter more commonly reported (25, 29, 31, 38, 50, 58, 68, 72, 98, 108, 133, 135, 148, 157, 165). Patients exhibiting neutrophilic pleocytosis tend to do so during the earlier stages of disease, frequently in association with a more acute clinical form of meningitis (25, 31, 58, 69, 122). The duration of persistence of CSF neutrophilia in patients exhibiting neutrophilic pleocytosis has not been well characterized, but periods ranging from days to weeks have been documented (69, 72, 98, 108, 135, 136).

Other potential infectious etiologies

The pathogens cited above are all well-established causes of persistent neutrophilic meningitis, as judged by our recent experience and that reported by others in the medical literature. In addition to this rather select group of etiologies, a number of other pathogens and infectious entities warrant consideration as potential causes of this syndrome, although documentation in the published literature of their role is lacking.

Partially treated pyogenic meningitis is a continuing diagnostic challenge to clinicians, since 25 to 50% of patients with suspected meningitis will already have received antibiotic therapy by the time the initial lumbar puncture is performed (111). Although prior therapy clearly reduces positive findings on Gram stain and culture, the CSF white cell count and differential count and the CSF protein and glucose values are usually not significantly altered by "nonmeningitis" doses of antibiotics (104, 111). Thus, such patients may exhibit neutrophilic CSF profiles with negative routine cultures. In these partially treated patients, detection of bacterial antigens by counterimmunoelectrophoresis or coagglutination may assist in identifying that subset with disease due to *S. pneumoniae*, *N. meningitidis* and *H. influenzae* (111). If antigen screens are negative but the epidemiologic setting and clinical findings still suggest bacterial infection, then additional therapy with appropriate parenteral antibiotics is frequently advocated (36, 111). Since common pyogenic bacteria are often etiologic in these cases, such therapy generally produces prompt improvement in both clinical status and CSF parameters. As would be seen in patients with typical bacterial meningitis, the evolution from CSF neutrophilia to a lymphocytic pleocytosis occurs over 24 to 72 hours (150). As such, these patients would rarely if ever exhibit persistent neutrophilic meningitis.

Suppurative parameningeal foci (e.g., brain abscess, subdural empyema, spinal epidural abscess, contiguous pyogenic inflammation, etc.) may be accompanied by signs of meningitis and CSF pleocytosis (158). Although the most typical CSF pattern may be the lymphocytic/normal glucose profile (86, 158), the CSF abnormalities are extremely variable and may on occasion mimic pyogenic meningitis (141). Parameningeal processes most commonly associated with purulent CSF profiles include subdural empyema in children (54), brain abscess with leakage or rupture into the ventricle

(158), and early bacterial cerebritis (158). If the parameningeal process extends to involve the meninges and subarachnoid space, then the typical CSF pattern of bacterial meningitis (i.e., neutrophilic pleocytosis with hypoglycorrhachia) is usually seen (10, 128, 141). Failure to recognize and drain the parameningeal focus definitively in such cases could lead to the syndrome of persistent neutrophilic meningitis since antibiotic therapy might "sterilize" the CSF but fail to eradicate the contiguous suppurative focus.

Viral CNS infections generally produce a lymphocytic/normal glucose CSF profile (86, 158). However, the early phase of viral meningoencephalitis may be characterized by a neutrophilic CSF response (158), with conversion to a lymphocytic pleocytosis generally occurring over the subsequent 6 to 24 hours (55). Selected viruses such as herpes simplex, mumps and lymphocytic choriomeningitis may produce an intense neutrophilic CSF response with hypoglycorrhachia, closely mimicking bacterial meningitis (99). Since the course of patients with herpes simplex encephalitis may extend over several weeks, it is conceivable that the syndrome of persistent neutrophilic meningitis might occur.

Rickettsial infection may occasionally be accompanied by neurologic manifestations. In patients with Rocky Mountain Spotted Fever, the most prevalent rickettsial disease, CNS abnormalities develop in approximately one-fourth of affected patients (90). CSF analysis yields variable findings but neutrophil predominance and hypoglycorrhachia occasionally are seen (90). However, the tempo of disease progression, particularly if untreated, would usually preclude development of chronic CNS syndromes such as persistent neutrophilic meningitis.

Certain fastidious microbes such as *Listeria monocytogenes* and the *Leptospira* species may on occasion produce poorly defined meningitic syndromes largely attributable to the difficulties encountered in the isolation of these organisms from the cerebrospinal fluid. Meningitis due to these organisms may be associated with a neutrophilic CSF profile (47, 82, 125). Since the fastidious growth requirements and slow growth rates of the organisms may delay definitive cultural isolation and identification beyond one week, the clinical setting may be that of persistent neutrophilic meningitis.

Protozoans are becoming increasingly recognized as etiologic causes of a wide variety of CNS syndromes, including meningitis. The majority of these agents tend to produce CSF profiles of the lymphocytic/normal glucose type (158). Representative protozoan CNS infections in this category include trichinosis (99, 158), toxoplasmosis (163) and cysticercosis (147). Protozoans most likely to produce neutrophilic CSF profiles include *Entamoebae histolytica* (107) and the *Naegleria* species (110). In general, the course of such cases is fulminant, with death usually occurring within seven days of onset. The rapidly fatal nature of these infections thus precludes their consideration as a cause of persistent neutrophilic meningitis. Granulomatous amebic meningoencephalitis due to *Acanthamoeba* may be associated with either a lymphocytic or neutrophilic pleocytosis (77, 110). The more chronic nature of this infection could conceivably lead to persistent CNS syndromes, but the majority would be expected to be accompanied by a lymphocytic cellular response (109).

Noninfectious etiologies

Although infectious etiologies are the predominant cause of persistent neutrophilic CSF profiles, several noninfectious entities warrant etiologic consideration as well (86, 158). The most likely potential noninfectious causes would include endogenous or exogenous chemical meningitis, hypersensitivity (drug-induced) meningitis, and immunologic diseases (86, 99, 158, 160).

Endogenous chemical meningitis results from the release of material into the CSF from intracranial tumors, usually craniopharyngiomas or epidermoids (86, 145). CSF findings may be chronic and include either neutrophilic or lymphocytic pleocytosis with hypoglycorrhachia (86, 145, 158). Exogenous chemical meningitis results from the introduction of trace amounts of detergents, disinfectants, contrast media or chemotherapeutic agents into the CSF during the course of diagnostic or therapeutic lumbar puncture (28, 52, 70, 86, 158, 160). CSF analysis usually reveals neutrophilic pleocytosis and hypoglycorrhachia (86, 99), which may persist even after the inciting stimulus has been withdrawn (28).

Drug-induced hypersensitivity syndromes are a well-recognized but rare cause of neutrophilic meningitis (86, 158, 160). Implicated agents have included sulfonamides (11), isoniazid (66), ibuprofen (22) and tolmetin (140). In most instances, discontinuation of the offending drug results in prompt resolution of the meningeal symptoms and signs, and persistent meningitis does not develop.

Selected immunologic diseases, complicated by meningitis or meningoencephalitis, may also exhibit the CSF profile of neutrophilic meningitis. In the initial stages of Mollaret's meningitis, almost all patients exhibit a neutrophilic pleocytosis (83, 160) but conversion to lymphocytic predominance usually occurs within 24–48 hours (83, 160). However, Swartz and Dodge (160) commented upon a

case of recurrent, possibly Mollaret's, meningitis in which the neutrophil predominance persisted for longer than one week on several occasions. Neuropsychiatric features, including meningitis, complicate systemic lupus erythematosus in 30 to 40% of cases (56), with CSF abnormalities evident in 30 to 50% of these patients (56, 80, 88). Pleocytosis has been observed in one-third of those with CSF abnormalities (56, 88). Although lymphocytes usually predominate (56, 88), there are numerous reports of patients with a neutrophilic CSF profile resembling bacterial meningitis (56, 62, 80, 88, 93). Marked fluctuations in CSF findings over time have also been noted, with alternating neutrophilic and lymphocytic pleocytosis. On occasion, the neutrophilic pleocytosis has been noted to persist over several months (62). Neurologic involvement in Behçet's syndrome occurs in 10 to 25% of patients (52, 154). CSF analysis in these patients generally reveals low-grade pleocytosis with either neutrophils or lymphocytes predominating (126, 144, 160). Persistence of neutrophils beyond several days has not as yet been documented (126, 160).

Carcinomatous meningitis is usually associated with lymphocytic rather than neutrophilic pleocytosis (86, 99, 158). However, a number of reviews of this topic clearly document the occurrence of neutrophilic pleocytosis in selected patients (85, 106, 127). Since CSF neutrophilia sometimes persists beyond one week in patients with carcinomatous meningitis, these patients may show clinical signs of persistent neutrophilic meningitis.

Pathogenesis of persisting CSF neutrophilia

Neutrophil chemotactic factors generally derive from the interaction of an organism and its products with various of the host defense systems, especially complement (169). In addition, certain bacterial proteins may directly function as chemoattractants for neutrophils (143), as can substances released from neutrophils themselves during degranulation (41). Although most invading organisms will generate a primary neutrophilic response, this response tends to wane and to be supplanted by mononuclear cells in cases of chronic or persistent disease due to intracellular pathogens (78). The exact nature of the event mediating conversion of the host cell response from neutrophilic to mononuclear is unknown. Most of the infectious agents listed in Table 3, many of which are intracellular pathogens, elicit an initial neutrophilic host response which would be supplanted by a mononuclear response in cases of persistent disease. For reasons that are unclear, this conversion to a mononuclear cell response did not occur in our reported patients with meningitis. One can only speculate that a continuing generation of neutrophil chemotactic factors occurred in these patients. Recent work by several investigators may provide a clue as to why certain of these intracellular pathogens may elicit a persisting neutrophil response. Schaffner et al recently reported that resistance to *Aspergillus* is mediated by two independent phagocytic cell lines, which form graded defense systems (142). The responding phagocytic cell line appears to be dictated by the morphologic form of the fungus—mononuclear cells provide protection against conidia whereas neutrophils respond to the presence of mycelial or hyphal elements. Since the morphologic form of *Aspergillus* in invasive disease is hyphae (17), the observations of Schaffner and colleagues may explain why the predominant phagocytic cell responding in such instances is neutrophilic. In that regard, microscopic examination of the leptomeninges of Case 1 at postmortem study revealed numerous hyphal elements. Likewise, studies by Diamond et al (43) suggest that neutrophils play an important role in human host defense against zygomycetes. Recent investigations by this group (34) have found that hyphal forms of *Rhizopus oryzae*, the most common cause of zygomycosis, appear to generate neutrophil chemotactic factors from serum. In addition, *Rhizopus* hyphae were also found to release a previously undescribed substance, which directly stimulated neutrophil chemotaxis in the absence of sera. Thus, these observations provide a potential explanation for the continuing neutrophilic CSF response in our patient with rhinocerebral zygomycosis.

Approach to the diagnosis of persistent neutrophilic meningitis

The exact incidence of persistent neutrophilic meningitis cannot be estimated on the basis of available data. As judged from our literature review, this problem is not rare. The true occurrence of persistent neutrophilic meningitis was probably underestimated in our review because many cases provided insufficient data to allow accurate determination of the duration of CSF neutrophilia. The cardinal feature of the syndrome is the persistence of neutrophils in the CSF over extended periods of time. The resultant clinical picture is that of "chronic" meningitis of neutrophilic rather than lymphocytic type. Diagnosis in many cases must be inferential, based upon the isolation of a potential causative agent from an extraneural site, or it must depend upon histopathologic and cultural evaluation of neural tissue obtained by invasive procedures. However, certain clinical findings may provide helpful clues about etiology (Table 4).

Clinical setting/host status: The clinical setting

TABLE 4. Useful diagnostic features in patients with persistent neutrophilic meningitis*

Potential Etiology (See Table 3)	Epidemiologic History†	Clinical Setting/ Host Deficits‡	Physical Findings			Abnormal Chest X-Ray	Special CSF Studies§	Abnormal Cranial CT‖	Biopsy of Extraneural Lesions/Sites¶
			Cutaneous Lesions	Oropharyngeal Disease	Fundoscopic Abnormalities				
Actinomycosis				±				+	
Nocardiosis		+(↓CMI)				±		+	+
Candidiasis		+(↓WBC)	+	+	+		+		+
Aspergillosis		+(↓WBC)		+		+	+	+	+
Zygomycosis		+(↓WBC)		+		+		+	+
Dematiomycosis			+					±	+
Brucellosis	+						±		+
Tuberculosis	+		±		±	+	+		+
Blastomycosis	+		+			+			+
Histoplasmosis	+			+		+	+		+
Coccidioidomycosis	+		+			+	+		+
Pseudoallescheriasis		+(↓WBC)				+		+	+
Chemical meningitis	+	+							
Systemic lupus erythematosus			+		+				

* Such features, if present, provide support for the listed etiology; exact occurrence of each feature in association with the listed etiology is impossible to estimate. CSF = cerebrospinal fluid. CT = computed tomography.

† Geographic location of residence, occupation, recent/remote travel history, exposure history, etc.

‡ Host deficits include neutropenia (↓WBC), impaired antibody synthesis (↓ab), and impaired cell mediated immunity (↓CMI).

§ Special CSF studies include wet preps, detection of metabolic byproducts, detection of specific antibody or antigen (See text).

‖ Scans demonstrating mass lesions or abscess.

¶ Biopsy of skin lesions, nodes, pulmonary lesions, liver, bone marrow.

in which disease occurs is of paramount importance. Since disease due to certain infectious agents is frequently associated with specific host immune deficits (7, 44, 84, 152), the nature of these deficits may provide important clues as to the potential etiology of complicating infection. For example, nocardiosis tends to occur more frequently in patients with impaired cell-mediated immunity (84, 102, 130), whereas invasive disease due to *Candida*, *Aspergillus* and *Rhizopus* frequently occurs in association with profound neutropenia (7, 152). Among noninfectious causes of persistent neutrophilic meningitis, both exogenous chemical meningitis and hypersensitivity meningitis occur in defined epidemiologic settings (e.g., after lumbar puncture or following drug administration). In patients with known multisystem disorders (e.g. systemic lupus erythematosus), the superimposition of meningeal symptoms and signs should raise the specter of CNS involvement with the primary disease process. Therefore, the setting in which disease occurs may offer important etiologic clues.

Clinical findings: The presence of accompanying clinical findings may also provide etiologic clues as to the nature of the underlying cause of meningitis. Although isolated CNS disease may be the only manifestation of infection, many of the agents listed in Table 3 produce multisystem disease. Presence of disease at other sites may either suggest a specific agent or provide a more accessible site for cultural and histopathologic evaluation than the CNS. Particular attention should thus be directed to examination of the eyes, oropharynx, mucous membranes, lungs, skin and lymph nodes in order to detect stigmata of local and disseminated disease (44, 52, 171). For most of the infectious entities under consideration, the pulmonary tree is the major portal of entry. When overt pulmonary disease occurs in association with CNS disease, evaluation of the nature of the pulmonary process (139) is often diagnostically more useful than evaluation of the CSF.

With disorders such as lupus erythematosus, the presence of multiorgan involvement provides a major cornerstone for diagnosis. Thus, if lupus is suspected in a patient with persistent neutrophilic meningitis, consideration should be given to biopsy of potentially involved extraneural organs (i.e., skin, kidneys) to aid in the establishment of a diagnosis.

Laboratory studies: Studies of peripheral blood are of limited usefulness in the evaluation of patients with persistent neutrophilic meningitis. Although antibody detection in serum may establish a diagnosis of extraneural disease and lend support to an inferential diagnosis of CNS disease, it is frequently neither definitive nor sensitive. A more promising technique is the detection of antigenemia (4, 167, 168), which may play an important role in the diagnosis of perplexing meningitides (30). Systemic diseases involving the CNS which are accompanied by characteristic serologic markers (e.g., systemic lupus erythematosus) might also be amenable to serologic diagnosis.

Although limited in availability and undefined as to exact role, special studies of CSF warrant consideration in these cases. Detection of characteristic metabolic byproducts of various organisms using gas-liquid chromatography (65, 75, 95) has rapidly evolved as a useful diagnostic technique and has potential appplicability to the diagnosis of infectious meningitis (26, 161). Likewise, detection of antibody in CSF has been employed with some diagnostic success, especially in cases of fungal meningitis. Plouffe and Fass reported on the use of CSF serologies in the diagnosis of *Histoplasma* meningitis and found that diagnostic rises in CSF antibody titers appear to occur only in patients with CNS involvement (133). It has also been shown in coccidioidomycosis with meningeal involvement that rises in CSF complement-fixation titers are a sensitive and specific diagnostic test (149). Experience with antigen detection in the diagnosis of CSF infection is confined primarily to pyogenic bacterial meningitis (37) and cryptococcal disease (73). However, detection of other fungal antigens (4, 167, 168) in CSF is now possible. In fact, detection of *Aspergillus* antigen in the CSF of Case 1 in this report (166) helped to confirm the diagnosis of CNS aspergillosis. In a similar fashion, a preliminary report has suggested a possible role for lymphocyte transformation in response to specific antigen (134) as a diagnostic test in cases of chronic infectious meningitis, but the exact role of this assay remains to be defined. Lastly, since carcinomatous meningitis may potentially produce persistent CSF neutrophilia, cytologic studies of CSF should be routinely pursued in patients with persistent neutrophilic meningitis. Such studies may also be helpful in the diagnosis of infectious entities as well (20).

Repetitive lumbar puncture: The role of serial lumbar punctures in the ongoing evaluation and management of the patient with typical bacterial meningitis is poorly defined (32, 45, 55, 129, 137). In the patient with persistent or chronic meningitis, serial lumbar punctures are crucial for the recognition of the syndrome. The finding that should stimulate the clinician to perform repeat lumbar puncture would be a poor clinical response to therapy, especially if a specific etiologic diagnosis had not been established. If sequential CSF studies then

reveal continuing neutrophilic pleocytosis, a diagnosis of persistent neutrophilic meningitis should be entertained with etiologic consideration given to the categories outlined in Tables 2 and 3.

Despite the low diagnostic yield of smears and cultures of CSF for most of the entities producing persistent neutrophilic meningitis (52, 112), these studies should nevertheless be done. As suggested by Ellner and Bennett, repetitive studies employing large volumes of CSF may increase the diagnostic yield (52). The clinician should routinely notify the microbiology laboratory that unusual or fastidious organisms (e.g., *Brucella*, *Nocardia*, *Actinomyces*, fungi, etc.) are potentially present, so that special culture techniques and prolonged incubation of cultures may be performed when indicated (51, 52). Since many of the special CSF studies alluded to above may not initially be considered, repeat CSF studies are often required to obtain fluid for these tests. Lastly, serial CSF studies provide a mechanism to monitor the status of the CNS process and evaluate response to empiric therapies.

Radiographic studies: Radiographic techniques have limited usefulness in the etiologic diagnosis of persistent neutrophilic meningitis, except to evaluate the possible coexistence of a cerebral mass lesion or abscess or the presence of other inflammatory parameningeal foci. Among available techniques, computed tomography appears to be most sensitive (53, 84, 123) and should be routinely employed in the evaluation of these patients. Since parameningeal disease may involve the spinal cord as well as the brain, consideration should be given to including the entire cord in addition to the brain in the CT evaluation. In patients with isolated leptomeningitis, abnormal gyral enhancement or obscuration of the basal cisterns by inflammatory tissue may be seen in the later phases of disease (123). Brain abscess typically appears as a circumscribed ring-shaped area of contrast enhancement (123), although the appearance of such lesions may be markedly attenuated in the immunocompromised host (53, 84, 123). The presence of persistent neutrophilic meningitis in association with a parenchymal brain lesion should strongly suggest the possibility of actinomycosis, nocardiosis, aspergillosis, pseudoallescheriasis, or zygomycosis (7, 84).

Tissue diagnosis: The role of invasive biopsy procedures in the diagnosis of persistent or chronic meningitis of any type remains controversial (52). Ellner and Bennett suggest that in the absence of demonstrable focal lesions, meningeal or brain biopsy is a low-yield procedure and should be reserved for those patients "undergoing indicated ventricular shunting, those with inexorable progression of disease or those with marked functional compromise despite adequate trials of therapy" (52). However, biopsy of meninges and brain is certainly indicated in those patients undergoing craniotomy for exploration of a mass lesion (51). Biopsy of suspicious extraneural lesions should be vigorously pursued in hopes of documenting the presence of disseminated or multisystem disease and thus inferentially diagnosing the CNS process (51, 52).

A summary of recommended diagnostic studies in the patient with persistent neutrophilic meningitis is shown in Table 5.

Approach to the therapy of the patient with persistent neutrophilic meningitis

Because of the relatively large number of potential etiologies and the diverse clinical settings in which persistent neutrophilic meningitis may occur, general therapeutic recommendations are impossible. Noninfectious etiologies should certainly be considered and excluded coincident with or before embarking upon any empiric trial of antimicrobic therapy. Discontinuing unnecessary medications may aid in the evaluation of potential hypersensitivity reactions. A careful review of epidemiologic parameters may allow identification and elimination of extrinsic causes of chemical meningitis in selected patients. A diagnosis of systemic lupus erythematosus may dictate a need for intervention with corticosteroids.

If noninfectious etiologies are excluded, and the patient's clinical status permits, all available diagnostic studies as outlined in Table 5 should be expeditiously performed prior to any consideration of therapy. However, in a patient with progressive neutrophilic meningitis unresponsive to routine antibacterial therapies, empiric treatment may be justified. If possible, such therapy should be based on clues suggested by epidemiology, clinical setting, physical findings or laboratory studies. The nature of host immunologic deficits, if any, should be a major determinant in drug selection (8, 84, 146). Particularly in the immunocompromised host, consideration should be given to the empiric use of amphotericin B with or without a sulfonamide.

Summary

Persistent neutrophilic meningitis is a poorly described variant of chronic meningitis characterized by the persistence of neutrophils in the CSF over extended periods of time (> 1 wk) in association with ongoing signs of meningeal inflammation and negative CSF cultures for bacteria and other pathogens. Although the incidence of persistent neutrophilic meningitis is difficult to ascertain, a review of available literature on CNS infections suggests that this entity is not rare. Etiologies of this syndrome are both infectious and noninfec-

TABLE 5. Diagnostic studies warranting consideration in the patient with persistent neutrophilic meningitis*

Test	Type Specimen or Target Site for Examination	Recommended Studies	Availability of Test†
Antibody titers	Serum	Brucella agglutinins	Routine
		Fungal serologies (complement fixation and immunodiffusion for *Blastomyces*, *Histoplasma* and *Coccidioides*)	Routine
		Antinuclear antibodies	Routine
	CSF	Fungal serologies (complement fixation and immunodiffusion for *Blastomyces*, *Histoplasma*, and *Coccidioides*)	Routine
Antigen assays	Serum	RIA or ELISA studies for *Candida* antigenemia	Experimental
		Latex agglutination studies for *Candida* antigenemia	Routine
		RIA studies for *Aspergillus* antigenemia	Experimental
	CSF	RIA studies for *Candida* and *Aspergillus* antigens	Experimental
Detection of metabolic by-products	CSF	GLC studies for detection of indoline or D-arabinitol	Experimental
Cytologies	CSF	Histopathologic studies for detection of fungi and malignant cells	Routine
Special cultures	CSF	Prolonged incubation (14–28 d)	Routine upon request
		Enriched CO_2 atmosphere (5%)	
		Special media	
Computed tomography	Head, spinal cord	Enhanced and unenhanced studies to exclude paramenigeal inflammatory foci	Routine
Tissue biopsies	Involved extraneural sites, leptomeninges	Histopathologic examination and culture of involved tissues	Routine

* CSF = Cerebrospinal fluid; RIA = Radioimmunoassay; ELISA = Enzyme-linked immunosorbent assay; GLC = Gas-liquid chromatography.

† Tests designated as routine are those generally available in all diagnostic laboratories; those designated as experimental are largely available only on a research basis.

tious. Among infectious causes, bacteria such as *Nocardia* and *Actinomyces* and systemic mycoses such as *Aspergillus* and the zygomycetes are the predominant pathogens. The pathogenesis of the persistent neutrophilic CSF response is unknown; with some infectious etiologies, there may be a correlation between neutrophil response and the morphology of the invading organism. Mycelial-like pathogens appear to be the primary stimulus for an ongoing neutrophilic inflammatory response. In cases of persistent neutrophilic meningitis, epidemiologic features and clinical setting frequently offer clues to the etiologic agent, especially in the immunocompromised host. Evaluation should include repetitive cultural and serologic studies of the CSF with special emphasis upon special cultural methods, antigen detection and detection of characteristic metabolic byproducts. Biopsy of extraneural sites of disease should be pursued whenever possible to provide data for an inferential diagnosis of CNS disease. CNS biopsies should be selectively performed in those patients undergoing craniotomy for evaluation of mass lesions. Therapy must be individualized. However, in the immunocompromised host, consideration should be given to the empiric use of amphotericin B with or without a sulfonamide in undiagnosed cases that manifest progressive clinical deterioration.

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