Inflammatory diseases of the CNS II: Meningitis and cerebral abscess

Introduction
Infections of the leptomeninges and subarachnoid space may arise as a consequence of viral, bacterial or fungal pathogens (table). Typically, organisms gain entry to the CNS through haematogenous spread from a systemic source of sepsis or through direct spread from the skull or as a complication of a surgical procedure. In this the second of a series of articles on the neuropathology of Inflammatory Diseases of the CNS we provide an overview of the approach to the neuropathological assessment of meningitis, illustrated with examples of the common abnormalities which may be encountered.

Background Circumstances
A vital component in the pathology assessment of any case is a review of all pertinent, clinical information. Thus, where meningitis is suspected clinically, information regarding the symptoms at presentation, intercurrent illnesses, immune status, prior medical history, results of all investigations and management of the acute presentation (particularly any antimicrobial therapy employed) should, ideally, be available to the reporting pathologist. This information then guides not only the appropriate course of further investigations but will also inform the health and safety procedures which should be employed in the mortuary and/or laboratory.

As noted, meningitis generally arises as a consequence of the direct or haematogenous spread of an organism to the CNS. Thus, in making as full an assessment as possible at autopsy it is preferable to perform a complete, ‘unlimited’ examination whereby all the major body cavities and organs are examined. However, if consent for an unlimited procedure cannot be obtained, it is still possible to perform a limited examination such as cranial cavity and contents only. Even in such limited examinations substantial information pertaining to the illness and its response to therapy can be obtained. Given this, where autopsy examination is desirable, it is often of value to discuss the case with a local pathologist prior to seeking consent from the next of kin. Common to all assessments of the brain in meningitis are a macroscopic inspection of the whole organ in situ, sampling of CSF/ tissue for culture, sectioning of the organ for further macroscopic examination (preferably after a suitable period of fixation) and sampling for histology.

Pathology
With these comments in mind regarding the general approach to autopsy examination in a case of suspected meningitis, we will now consider the typical patterns of pathology encountered and the common causative organisms involved.

Aseptic Meningitis
Aseptic meningitis describes a characteristically short-lived illness marked by headache, photophobia and neck stiffness. Typically, examination of CSF reveals a cellular specimen with the predominant cell type being lymphocytes, though in the early stages polymorphs may be present. In the great majority of cases (80% or more) the causative organism is a non-polio enterovirus though a number of other agents including a wide range of viruses, bacteria and drug reactions have been implicated1. Whilst CNS involvement is typically benign, occasional cases do appear at autopsy as a consequence of systemic manifestations of the pathogen (usually viral) such as myocarditis with associated arrhythmia and sudden death. Where described the pathology is of a normal or minimally swollen brain to naked eye examination. On histological inspection a mild lymphocytic infiltrate in the meninges and superficial perivascular spaces is typical.

Purulent (Acute Bacterial) Meningitis
A variety of bacterial species may give rise to purulent meningitis with the likely causative organism influenced by the age of the patient and their immune status (table). As such, in immunocompetent adults the commonest causative organism identified are Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae B. These share a number of characteristics that contribute to both their incidence and their pathogenicity. They are commensal bacteria which are frequently isolated in samples from the nasopharynx of asymptomatic carriers. Furthermore, these organisms have a polysaccharide capsule that renders them resistant to macrophage digestion. Finally, they are capable of releasing a number of proinflammatory products which stimulate cytokine production and release from nearby endothelial cells and macrophages. This latter process culminates in the release of potent chemottractants

Table: Common organisms associated with meningitis

| Aseptic meningitis | non-polio enteroviruses, Herpes simplex virus 2, mumps, human immunodeficiency virus |
| Purulent meningitis | group B streptococci, Escherichia coli, Klebsiella species, Listeria monocytogenes |
| Adults | Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis |
| Granulomatous | Mycobacterium tuberculosis |
| Immune compromised | above + fungal (Cryptococcus neoformans, Candida species, Aspergillus) |

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resulting in the migration of numerous neutrophil polymorphs to the region of infection, a characteristic feature of pyogenic infections. On cytological examination of CSF, there is, as might be expected, a florid neutrophil leukocytosis.

At autopsy the brain may appear diffusely swollen as a consequence both of oedema and hydrocephalus. Reflecting the dura reveals congested meningeal vessels and a typically purulent exudate more pronounced in the Sylvian fissures and over the base of the brain (fig. 2a). Frequently, evidence of obstruction to flow of CSF with associated hydrocephalus is present. On microscopy a meningeal inflammatory infiltrate consisting of lymphocytes, macrophages and granulomas composed of a central area of necrosis surrounded by epithelioid macrophages and lymphocytes is described (fig. 2b). In contrast to similar lesions which may be encountered elsewhere in the body, Langhan's giant cells can be infrequent in tubercle-related granulomas in the CNS.

Meningitis in the Immunocompromised

In general the incidence of the commoner organisms associated with purulent and granulomatous meningitis is increased in the immunocompromised state. This is typified by the increased risk of pneumococcal infection which follows splenectomy and the increased incidence of tuberculous meningitis with AIDS. In addition, however, a number of other organisms rarely encountered in the immunocompetent may arise. Amongst these are the fungal pathogens of which Cryptococcus neoformans, Candida albicans, and Aspergillus fumigatus are most commonly associated with meningitis. Cryptococcal meningitis is noteworthy as the commonest mycosis associated with AIDS. On examination of CSF in cryptococcal meningitis the thickly encapsulated yeasts can occasionally be detected on staining the specimen with Indian ink. At autopsy the typical picture is of a pale yellow meningeal exudate over the vertex with multiple, small, mucoid, perivascular, ‘soap bubble’ cysts within the deep grey matter (fig. 3a). The histological picture varies from a mild meningeal inflammatory cell infiltrate through to a florid, granulomatous reaction with the inflammatory response in part dependent on the immune status of the host. Using appropriate stains the typical encapsulated organisms are readily identified (fig. 3b).
Cerebral Abscess
As with meningitis cerebral abscesses may arise as a consequence of direct spread from an adjacent source of infection or through haematogenous spread from elsewhere. Often the pattern of involvement and aetiological organisms reflect this distinction. Thus where the abscess arises as a consequence of direct spread, for example from a paranasal sinuses, the lesion is most often solitary, adjacent to the site of the primary infection and associated with a typical isolate (e.g. Streptococcus milleri). In contrast abscesses of haematogenous origin are often multiple, centred on the grey/white boundary and are most common within the distribution of the middle cerebral artery reflecting their embolic nature. Risk factors associated with such cerebral abscesses include bacterial endocarditis, chronic pulmonary sepsis, cyanotic congenital heart disease and intravenous drug abuse. As such the range of pathogens reflects the source of infection with streptococci and staphylococci most commonly isolated. At autopsy the appearances vary depending on the age of the lesion with early lesions poorly demarcated and associated with focal swelling. As the lesion matures the typical picture develops of a fibrous capsule around a well-demarcated, purulent core.

References