American Association of Neuropathologists

Emerging Viral Infections

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Case-Based Questions (please see page 3 for answers)

1.	Which of the following viruses is an emerging cause of arboviral encephalitis?	
	a.	Coxsackievirus B3 (CVB3)
	b.	Lassa virus (LASV)
	c.	Lymphocytic choriomeningitis virus (LCMV)
	d.	Orf virus (ORFV))
	e.	Oropouche virus (OROV)

2.	What histological findings are most suggestive of viral encephalitis?	
	a.	Eosinophilic meningitis
	b.	Macrophages with PAS-positive granules
	c.	Microglial nodules and neuronophagia
	d.	Necrotizing granulomatous inflammation
	e.	Neutrophilic inflammation and necrosis

3.	What is the best test for correctly identifying a specific cause of arboviral encephalitis in a patient being treated with rituximab for which a panel of CSF IgM tests is negative?	
	a.	16S rRNA sequencing
	b.	LFB-PAS (Luxol Fast Blue-Periodic Acid Schiff) staining
	c.	Metagenomic next-generation sequencing
	d.	Plasma cell free DNA testing
	e.	Transmission electron microscopy

Scroll to Page 3 for answers

Correct Answers and Rationales

Question 1 Correct Answer and Rationale**: E. Oropouche virus (OROV)**

Rationale: Oropouche virus (OROV) is an orthobunyavirus associated with encephalitis that is spread through biting midges and mosquitoes (arthropod-borne).

Coxsackievirus B3 is an enterovirus spread via fecal-oral route, respiratory droplets, or direct contact, Lassa virus and Lymphocytic choriomeningitis virus are arenaviruses spread by urine or fomites, and Orf virus is a parapoxvirus spread by contact.

Question 2 Correct Answer and Rationale: **C. Microglial nodules and neuronophagia**

Rationale: Microglial nodules and neuronophagia are features seen in many viral infections in the brain along with lymphohistiocytic perivascular and leptomeningeal inflammation.

Eosinophilic meningitis is more commonly seen with parasitic infections (e.g. angiostrongyliasis), macrophages with PAS-positive granules in Whipple's disease, necrotizing granulomatous inflammation with tuberculosis, and neutrophilic inflammation and necrosis with bacterial abscess.

Question 3 Correct Answer and Rationale: **C. Metagenomic next-generation sequencing**

Rationale: Metagenomic next-generation sequencing (mNGS) can detect any infection with sufficient RNA or DNA present in the specimen being tested (e.g. brain tissue or CSF). mNGS is often the test of choice for patients that are B-cell depleted and do not produce sufficient IgM, which is the preferred test in immunocompetent patients that tend to have shorter viremic windows for detection of arbovirus RNA, particularly when a large variety of causative organisms remain in the differential and individual targeted testing is limited by cost or available sample volume.

16S rRNA sequencing can be used to identify bacterial species. LFB-PAS can be used to detect demyelinating conditions including JC polyomavirus-associated progressive multifocal leukoencephalopathy. Plasma cell free DNA testing will not detect RNA viruses including arboviruses. Transmission electron microscopy may detect viral particles but is unable to identify specific viruses without immunogold labeling or other specialized techniques.