American Association of Neuropathologists

The Effects of Toxins and Therapies on the CNS: Neuropathological Aspects

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

1.	A 50-year-old woman with acute lymphoblastic leukemia treated with intrathecal methotrexate develops subacute confusion. MRI shows diffuse periventricular white matter T2 hyperintensities. What are the most characteristic histopathological features of Methotrexate-induced leukoencephalopathy?	
	a.	Alzheimer type II astrocytosis
	b.	Diffuse white matter vacuolation with oligodendrocyte loss
	c.	Multifocal microabscesses with neutrophils
	d.	Selective cortical neuronal loss with laminar necrosis
	e.	Widespread lymphocytic encephalitis

2.	A 48-year-old man with alcohol use disorder resorts to drinking antifreeze fluid from his garage. He develops rapidly progressive confusion and somnolence eventually leading to death. What is the most likely histopathological feature and toxic agent involved?	
	a.	Axonal degeneration of large nerve fibers – arsenic
	b.	Birefringent calcium oxalate deposits – ethylene glycol
	c.	Chromatolysis of motor neurons – thallium
	d.	Intracellular deposits in neurons – mercury

3.	A 65-year-old man with metastatic melanoma on nivolumab presents 8 weeks after therapy initiation with confusion, aphasia, and MRI T2/FLAIR hyperintensities in bilateral mesial temporal lobes. What is the most likely neuropathological finding?	
	a.	Extensive demyelination with oligodendrocyte loss
	b.	Granulomatous inflammation with multinucleated giant cells
	c.	Neutrophilic predominant inflammation
	d.	T-cell–predominant perivascular and parenchymal infiltrates
	e.	Spongiform change in gray and white matter

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Correct Answers and Rationales

Question 1 Correct Answer and Rationale**: B. Diffuse white matter vacuolation with oligodendrocyte loss**

Rationale: Methotrexate and other high-dose chemotherapy agents can cause diffuse white matter vacuolation with myelin pallor, oligodendrocyte loss and prominent spongiosis, in some cases with necrosis. There is usually a paucity of inflammation and collections of markedly swollen axons with dystrophic calcifications can be seen.

Question 2 Correct Answer and Rationale: **B. Birefringent calcium oxalate deposits – ethylene glycol**

Rationale: Antifreeze fluid often contains ethylene glycol. Characteristic birefringent calcium oxalate deposits can usually be demonstrated by polarized light microscopy in parenchymal and meningeal vessels.

Question 3 Correct Answer and Rationale: **D. T-cell–predominant perivascular and parenchymal infiltrates**

Rationale: Immune checkpoint inhibitor–associated encephalitis typically shows a perivascular and parenchymal lymphocytic infiltrate, mainly CD3+ T-cells, sometimes with neuronophagia.