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Commentary

Aseptic Meningitis may be Erroneously Diagnosed if CSF Cultures, Gram Stains, and Multiplex PCRs Produce False Negative Results

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Commentary

We read with interest the article by Jo *et al.* regarding two patients who developed meningitis 7 and 6 hours, respectively, after spinal anesthesia with bupivacaine; the condition was classified as drug-induced aseptic meningitis (DIAM) after bacterial and viral causes had been ruled out via cerebrospinal fluid (CSF) cultures (in both patients), CSF Gram staining (in patient 1), and multiplex PCR panels (in both patients) ^[1]. Both patients recovered completely following the administration of empirical antibiotics (ceftriaxone, vancomycin, and dexamethasone for patient 1) ^[1]. Certain aspects warrant discussion.

A first point is that the specific multiplex PCR methods used were not specified ^[1]. Which pathogens were detected by these tests? Had the multiplex PCR tests expired? Were the same tests used for both patients? Which manufacturer produced them? What are the sensitivity and specificity of these tests? The pooled sensitivity of multiplex PCR methods is reported to be 86–94%, indicating that approximately 10% of pathogens are not detected by this method ^[2].

A second point is that certain bacteria in the CSF are difficult to culture ^[3]. These include *Mycobacterium tuberculosis*, *Mycoplasma* species, *Cutibacterium acnes*, and *Leptospira* species ^[3]. Accordingly, the pooled sensitivity of CSF cultures is reported to be only 60–90% ^[4].

A third point is that no blood cultures were reported for either patient ^[1]. Given that both patients exhibited leucocytosis and Patient 1 also had elevated procalcitonin levels, obtaining blood cultures would have been essential, even though the clinical presentation in both cases was meningitis.

A fourth point is that no data regarding cerebrospinal fluid (CSF) C-reactive protein (CRP) levels are available ^[1]. It has recently been demonstrated that CSF CRP levels are a highly reliable predictor of bacterial meningitis ^[5].

A fifth point is that neither the residual contents of the ampoules used nor unused ampoules from the same batch were tested for contamination ^[1]. The fact that no further cases of meningitis occurred at the hospital after the affected batch was discarded suggests that the ampoules were contaminated.

Overall, bupivacaine should not be implicated as the cause of DIAM (drug-induced aseptic meningitis) in patients with pleocytosis and leukocytosis unless all potential infectious causes have been conclusively ruled out. Negative CSF cultures, negative Gram stains, and negative multiplex PCR results do not necessarily rule out infectious meningitis. Factors arguing against DIAM include the fact that both patients exhibited granulocytic pleocytosis and leukocytosis, as well as the fact that both recovered following antibiotic treatment.

Declarations**Ethical Approval:** Not applicable.**Consent to Participation:** Not applicable.**Consent for Publication:** Not applicable.**Funding:** None received.**Availability of Data and Material:** All data are available from the corresponding author.**Completing Interests:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.**Author Contribution:** JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval. xx: contributed to literature search, discussion, correction, and final approval.**Acknowledgements:** None.**Keywords:** Aseptic Meningitis, Pleocytosis, Bupivacaine, Drug-Induced, CSF Culture**References**

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