Nepal Journal of Neurosciences 2019;19(3):72-75

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Date of submission: 4th October 2018
Date of acceptance: 9th December 2019

DOI: https://doi.org:10.3126/njn.v19i3.27365

HOW TO CITE
Maurya PK, Shukla S, Tiwari A, Kulshreshtha D, Singh AK, Intractable Headache in a Patient with Carcinoma Breast: Infiltrative or Infective-A Diagnostic Challenge. NJNS 2019;19(3):72-75

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Intractable Headache in a Patient with Carcinoma Breast: Infiltrative or Infective - A Diagnostic Challenge

Chronic meningitis is the inflammation of meninges having varied clinical manifestations and diverse etiologies. Among them tuberculosis continues to be an important cause of chronic meningitis. To achieve the etiological diagnosis, examination of cerebrospinal fluid is mandatory. Carcinomatous meningitis, another rare cause of chronic meningitis is caused by infiltration of leptomeninges by malignant cells. Diagnostic gold standard of carcinomatous meningitis is to demonstrate malignant cells in the cerebrospinal fluid. In cerebrospinal fluid negative cases with high degree of suspicion, various biomarkers may assist to arrive at diagnosis. However examination of single sample, delayed processing and low volume cerebrospinal fluid analysis may give rise to false negative results. We report a patient of breast carcinoma presenting with intractable headache misdiagnosed as tuberculous meningitis. Definitive diagnosis of carcinomatous meningitis was established by repeated lumbar puncture and large volume of cerebrospinal fluid was sent for immediate processing. Our case emphasizes the importance of the above parameters of cerebrospinal fluid study to maximize the diagnostic accuracy and efficiency.

Key words: Carcinomatous meningitis, Cerebrospinal fluid, Headache, Lumbar puncture, Tuberculous meningitis

Chronic meningitis is the inflammation of meninges and has varied manifestation, diverse etiologies. In our subcontinent tuberculous meningitis is an important cause of chronic meningitis and sometimes clinicians have to give empirical antitubercular treatment, awaiting mycobacterial culture report. Whereas carcinomatous meningitis (CM) is another cause of chronic meningitis caused by infiltration of leptomeninges (pia, arachnoid) by malignant cells, a rare complication of malignancy. Demonstration of malignant cells in cerebrospinal fluid (CSF) is confirmatory. Sometimes the diagnosis of CM may be challenging due to persistently negative CSF cytology. In such cases, various organ specific and nonspecific biomarkers in CSF with variable sensitivity and specificity may assist in diagnosis. It is important to note that the positivity of CSF also depends on volume sent for analysis and serial lumbar puncture if previous one is negative. Delayed processing of sample often leads to loss of cell viability. We report a patient of breast carcinoma presenting with intractable headache misdiagnosed as tuberculous meningitis. The definitive diagnosis of carcinomatous meningitis was established by repeated lumbar puncture with analysis of large volume of cerebrospinal fluid and immediate processing.

Case Report

A 36-year-old lady presented with severe, worsening holocranial headache and low grade pyrexia for two months. She had associated nausea, vomiting and two episodes of generalised tonic clonic seizure. She was diagnosed as a case of adenocarcinoma breast (stage T3N1M0) for which she underwent surgery one year back and was advised oral Tamoxifen. She was evaluated by local physician for new onset headache and seizure. Her magnetic resonance imaging (MRI) brain was normal while CSF revealed lymphocytic pleocytosis, elevated protein and normal sugars which were suggestive of chronic meningitis. Due to suspicion of tuberculous meningitis, as it is the most common chronic meningitis in India, antitubercular drugs and steroids were initiated but her headache continued to worsen. On evaluation at our institute she was conscious and her fundus and cranial nerves were normal. Neck rigidity was positive. Motor and sensory examination was unremarkable. A repeat CSF examination showed elevated CSF pressure (290 mm of water) with < 5 mononuclear cells, low sugar (34 mg/dl) and elevated proteins (91 mg/dl). CSF culture, Gene Xpert test for mycobacterium tuberculosis and cryptococcal antigen test were negative. Hence, with a possibility of carcinomatous meningitis repeat contrast MRI brain was performed which revealed a small nodular enhancing lesion in left cerebellum and MR venography was normal (Figure 1a). Lumbar puncture (LP) was performed once again and large volume of CSF (10 ml) was sent for immediate analysis and malignant cells were identified in the sample (Figure1 b-d). She was transferred to oncology unit and treated with chemotherapy with partial improvement of headache at one month follow up.

Discussion

CM is known to be found in approximately 4-7% of solid tumours, among which breast, lung and malignant melanoma are more common[1]. Clinical manifestations are variable owing to multifocal involvement of brain, spinal cord and their exiting nerve roots[2,3]. The diagnostic gold standard is identification of malignant cells in CSF. To get optimal yield from CSF examination there are two important things to note, one is the volume of CSF and the other is repeated LP. The sensitivity of CSF cytology increases from 60% to 97% when 3.5 ml and 10.5 ml CSF are analysed respectively[4]. On second LP the sensitivity increases to 80% while it is estimated to be as low as 45-55% after first LP[3]. After the third lumbar puncture, there is only a very little benefit obtained.

In our patient first CSF sample at our centre was normal except for elevated intracranial pressure. The second large volume CSF sample was positive for malignant cells which emphasizes the importance of repeat LP and amount of sample. The Gd-MRI is imaging of choice in CM in the modern era and it may reveal typical findings as leptomeningeal enhancement and nodular deposits[5]. Repeat gadolinium enhanced MRI brain in our case revealed nodular enhancing lesion in cerebellum which further indicated towards malignant deposits to be the likely cause. However in frequent CSF negative cases, a variety of non-specific and organ specific biomarkers may be tested to support the diagnosis. These CSF biomarkers differ in sensitivity and specificity. Non-specific markers include β glucuronidase, lactate dehydrogenase, beta-2 microglobulin, carcinoembryonic antigen. Organ specific markers comprise of CA 15-3, CA 125, CA 19-9, CA 724, AFP, NSE, Cyfra 21-1 and EGFR[2,6]. Despite recent advances, the CSF positivity for malignant cells remains the gold standard test. Emphasis is to be given on early processing of CSF sample, as delaying the process can lead to loss of cell viability. 50% of cells remain viable after a delay of 30 minutes while this further decreases to 10% after a lag of 90 minutes between sample procurement and processing[7].

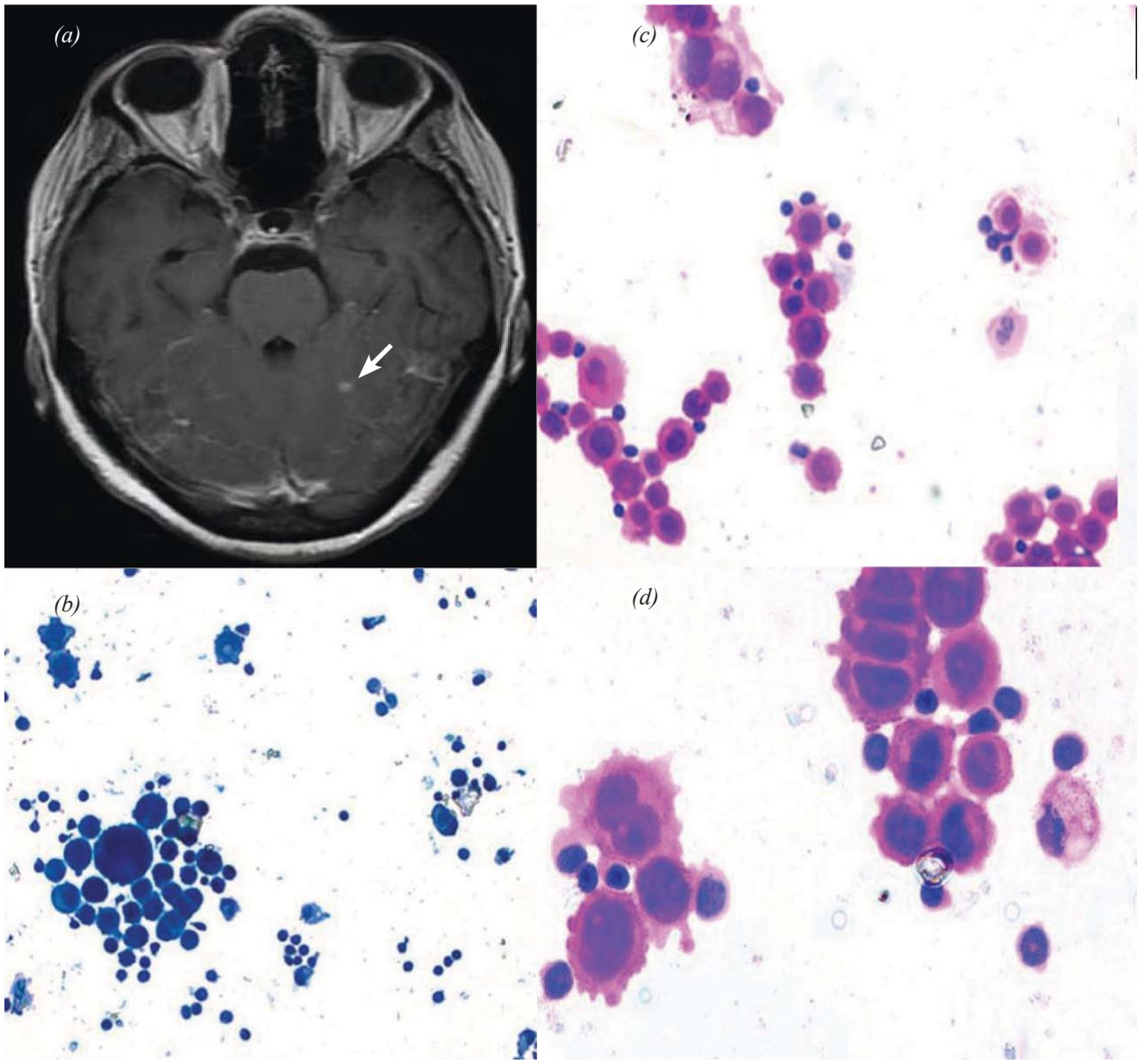

Figure 1(a): Magnetic resonance imaging brain T1 axial post contrast image demonstrating small nodular enhancing lesion in left cerebellum (arrow).

Figure 1(b-d): Cerebrospinal fluid sediment smears: Cellular smears show singly scattered and loosely cohesive clusters of atypical cells. The cells have pleomorphic nuclei with irregular nuclear membranes and moderate to scant amount of cytoplasm. Mononuclear inflammatory cells are identified in the background. (b=PAPx100, c=H&Ex200, d=H&Ex400).

Conclusion

In summary our case highlights the diagnostic challenges in establishing the diagnosis of CM in a patient with carcinoma breast. In a suspected case of CM, significance of early processing of large CSF volume and repeated lumbar puncture remains crucial for correct diagnosis and appropriate treatment.

Conflict of interest: None of the authors have potential conflicts of interest to be disclosed.

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