Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Breast cancer's hidden partner: meningoencephalitis as a paraneoplastic revelation: a rare presentation of invasive ductal carcinoma of breast: a case report

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Introduction and importance: Paraneoplastic neurologic syndromes encompass a group of neurologic disorders arising from pathological processes unrelated to metastasis, metabolic disturbances, infections, coagulopathy, or treatment-related side effects. These syndromes can affect various regions of the nervous system, resulting in diverse clinical manifestations

Case presentation: The authors present a rare case of anti-amphiphysin-associated meningoencephalitis in a South Asian Pakistani woman. Initially, the patient was managed for suspected infectious meningitis, but empirical treatment failed to yield improvement. Subsequent investigations unveiled a paraneoplastic syndrome secondary to breast cancer.

Discussion: Diagnosing these clinical entities is challenging due to their multifaceted presentations, often leading to delayed identification, increased patient suffering, economic burdens, and preventable complications.

Conclusion: Anti-amphiphysin-associated meningoencephalitis is a rare manifestation of paraneoplastic syndromes. It is crucial to raise awareness among healthcare professionals about the diverse presentations of paraneoplastic syndromes.

Keywords: anti amphiphysin, atypical presentation, autoimmune meningoencephalitis, breast carcinoma, corticosteroids, diagnostic masquerade, invasive ductal carcinoma, paraneoplastic neurological syndrome

Introduction

Paraneoplastic neurologic syndromes (PNS) refer to a set of neurologic illnesses caused by pathological processes other than metastatic spread, metabolic and nutritional deficits, infections, coagulopathy, or cancer therapy side effects[1,2]. PNS is a rare disease having an incidence of 1.22/100 000 persons per year and a prevalence of 4 per 100 000 per year[3].

Moreover, it is worth mentioning that the incidence of PNS is increasing due to improved diagnostic modalities. The classical presentation of PNS includes stiffness, rigidity, confusion, and cognitive dysfunction. Encephalitis is counted to be among the most high-risk phenotypes of PNS. This is usually seen in the setting of a malignant tumour. Occasionally, it is also related to benign conditions like demyelinating diseases.

These diseases can affect various regions of the nervous system such as the cerebral cortex, cerebellum, spinal cord, optic nerve, and neuromuscular junction. Clinically they can manifest as limbic encephalitis, brainstem encephalitis, rapidly progressive cerebellar syndrome, encephalomyelitis, myelitis, motor neuronopathy, stiff-person syndrome, opsoclonus-myoclonus, Lambert-Eaton myasthenic syndrome, myasthenia gravis, optic neuropathy, uveal melanocytic proliferation, and retinopathy. Owing to their varying and complex presentation, it is difficult to diagnose these clinical entities. Additionally, PNS can also be associated with various onconeural antibodies such as anti-amphiphysin antibodies. Amphiphysin, one of the onconeural antigens, is usually found in breast cancer and small-cell lung carcinoma[4]. In the case of PNS, anti-amphiphysin antibodies are commonly associated with myeloencephalitis and limbic encephalitis. However, to the best of our knowledge, no case of meningoencephalitis has been reported yet. This article presents a

HIGHLIGHTS

- Breast cancer can reveal itself through unexpected neurological symptoms.
- It is complicated and difficult to identify uncommon paraneoplastic conditions like anti-amphiphysin related meningoencephalitis in breast cancer.
- Interspecialty collaboration between oncologists and neurologists is crucial for effective patient care.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

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Annals of Medicine & Surgery (2024) 86:512–516

Received 24 September 2023; Accepted 3 November 2023

Published online 16 November 2023

http://dx.doi.org/10.1097/MS9.0000000000001499

rare clinical manifestation of PNS presenting as coexisting meningoencephalitis along with positive anti-amphiphysin antibodies.

Case report

A 54-year-old female, known case of hypertension and type 1 diabetes mellitus was admitted to a local hospital for altered mental status. Her chief complaints included fever, drowsiness, confusion, and slurred speech for the last 5 days. On examination, she was not oriented to time and place. Her Glasgow coma scale was 12/15. There was neck rigidity on flexion, facial twitching, and a deviated angle of mouth towards the right with drooling of saliva. The rest of the physical examination was unremarkable. Her history was significant for a breast lump in her left breast tissue for which she did not seek treatment. Based on her current presentation, a provisional diagnosis of infectious meningitis was established, and she was started on empiric antimicrobial therapy. She also received valproic acid for facial twitching. Meanwhile, laboratory and imaging studies were performed to evaluate her condition. The results of these investigations are summarized below.

An MRI scan of the brain was performed which showed a patchy meningeal enhancement along the bilateral lateral convexity of the cerebral hemisphere. It was associated with diffusion restriction in the right frontal region. These findings were suggestive of meningitis with focal right frontal encephalitis which explained the signs of confusion, slurred speech, and facial twitching due to inflammation of associated areas in frontal lobe. Images are as illustrated in Fig. 1.

Cerebrospinal fluid (CSF) analysis showed elevated glucose (210 g/dl) and protein levels (145 g/dl). The white blood cell count was 15 cells/ml. The details of the CSF analysis are described in Table 1. Furthermore, the electroencephalography (EEG) was normal. Consequently, her antimicrobial therapy was tailored for the treatment of viral meningoencephalitis. However, there was no improvement observed in her condition and her confusion even worsened to the point that she could no longer recognize her family. As her laboratory investigation results were negative for any infectious cause of meningoencephalitis, the focus shifted towards ruling out other differential diagnoses. Therefore, paraneoplastic workup was performed which revealed that anti-amphiphysin antibodies were positive as shown in Table 1.

Considering her history of a breast lump it was decided to evaluate the possibility of malignancy arising from the breast tissue. Therefore, she underwent ultrasonography and mammography to evaluate the breast lump. The ultrasonography of the breast tissue revealed an ill-defined mixed echogenicity lesion in the breast parenchyma causing surrounding architecture distortion and micro-lobulated margins. It also showed increased flow on colour doppler. It had both solid and cystic components. The overlying skin appeared thickened. The mammography revealed a lump and scattered coarse microcalcifications. The ultrasonographic and mammographic findings are illustrated in images A and B of Fig. 2:

Afterward, the patient underwent a core cut biopsy followed by histopathological examination which revealed invasive ductal carcinoma. The histopathological findings are illustrated in Fig. 3:

Meanwhile, she was started on intravenous methylprednisolone (1000 mg/day). On the third day, her orientation, sensorium, and speech improved. Intravenous methylprednisolone therapy was continued for 5 days followed by a tapering dose of oral prednisolone (30 mg/day). After a week, she was shifted from the intensive care unit to the general surgery floor for her future care related to breast cancer. She was advised to continue prednisone and have a regular follow-up with the neurologist. She did not report any exacerbation of neurologic problems in the subsequent follow-up visits. However, she complained of residual problems of insomnia, irritability, and walking instability. There was no improvement seen in these residual symptoms in the subsequent follow-up visits.

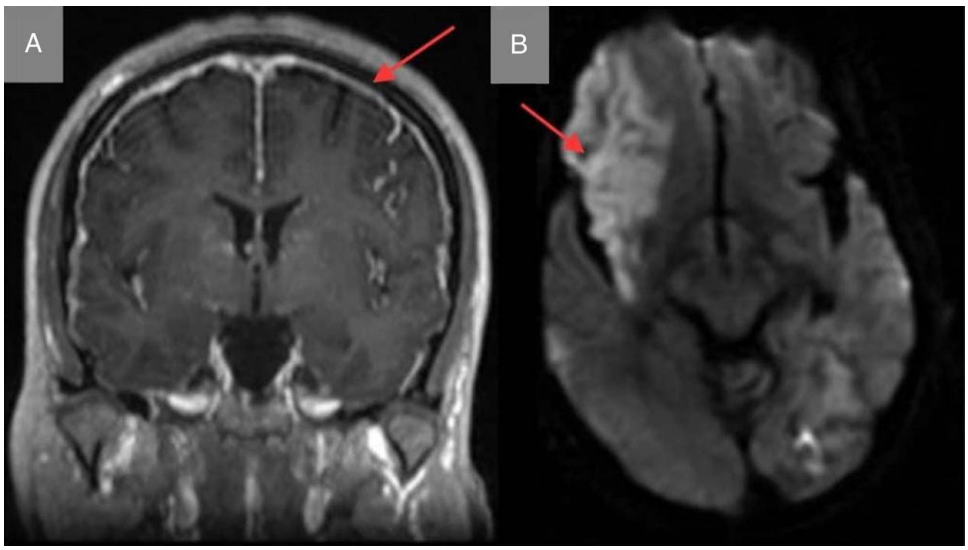

Figure 1. The findings of an MRI scan of the brain showing pachymeningeal enhancement seen along bilateral lateral convexity of the cerebral hemisphere as depicted by the red arrows in (A) and (B).

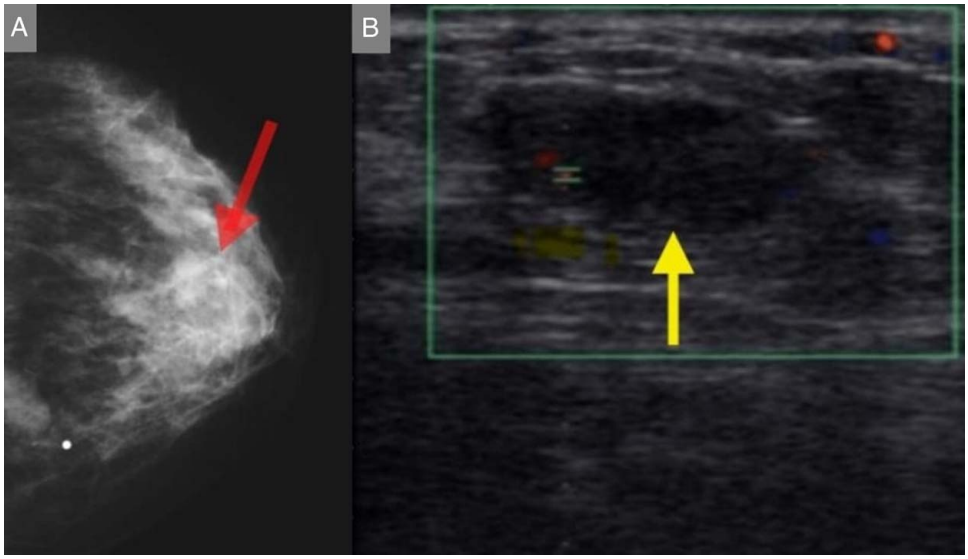

Figure 2. The red arrow in (A) illustrates the mammographic findings showing a lump and scattered coarse microcalcifications. The findings of ultrasonography of the left breast show an ill-defined mixed echogenicity lesion noted in the breast parenchyma as depicted by the yellow arrow in (B).

Discussion

The pathophysiological basis of paraneoplastic neurologic syndromes is not fully explained yet; However, an immunological mechanism is believed to be the underlying aetiology for the development of these disorders. It is postulated that dysfunction in the central nervous system can be caused by the formation of autoantibodies and t-cell responses against nervous system antigens. In cases of paraneoplastic syndrome, the immune system causes damage against common antigens that are shared by both the tumour and the nervous system[5].

The clinical presentation of anti-amphiphysin antibody-associated diseases is heterogeneous, which can make it difficult to diagnose and treat. Furthermore, keeping in view the vast number of differentials for such symptoms, there is a higher risk of misdiagnosis. In 2021 the American Academy of Neurology had revised diagnostic criteria for PNS to prevent the risk of misdiagnosis. As per this criteria, the case under discussion had

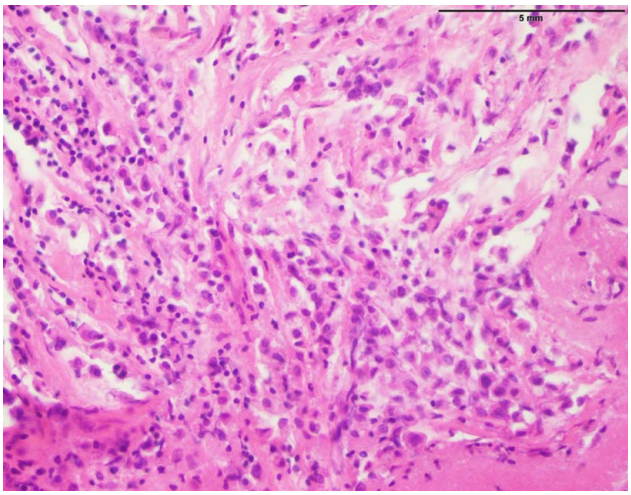

Figure 3. Hematoxylin and eosin shows infiltrative tumour cells. Cells are dyscohesive and arranged in cords and single-file patterns. Nuclear pleomorphism is noted. No duct formation is seen.

Table 1

Paraneoplastic workup

CSF analysis

Test	Result	Reference range
CSF glucose	210 mg/dl	40–70
CSF chloride	145 mmol/l	122–132
CSF protein	145 mg/100 ml	15–40
Appearance	Turbid	
CSF RBC	14/mm^3	0
CSF TLC	15/mm^3	0–5
CSF neutrophils	75%	0–24
CSF lymphocytes	25%	
CSF Pus cells	numerous	
Biofire syndromes test		
Biofire	Negative	
Paraneoplastic antibody panel		
Antigen	Intensity	Class
Amphiphysin (Amp)	36	+ +
CV2 (CV2)	3	0
PNMA2/Ta (Ma2/Ta)	1	0
Ri (Ri)	1	0
Yo (Yo)	2	0
Hu (Hu)	3	0
Recoverin (Rec)	2	0
SOX1(SOX1)	2	0
Titin (Titin)	3	0
Control (Co)	109	+ + +
Label (La)	-1	0

0–5 intensity is classified as 0 (negative), 6–10 as (+) (borderline), 11–25 as + (positive), 26–50 as + + (positive), 51–256 as + + + (strong positive).
CSF, cerebrospinal fluid; RBC, red blood cell.

a diagnostic score of 10 which proved it to be definitive PNS[6].

A recent study by Sun *et al.*[7], presented a case in which the patient was suffering from encephalitis secondary to invasive ductal carcinoma. However, in the study by Sun *et al.*[7] the neurological symptoms developed after the removal of the tumour. Conversely, in our case, neurological symptoms appeared even before the establishment of the diagnosis.

As far as the age at presentation is concerned, a study found that the median age was 52 years (with a range of 29–78), which is consistent with our case study in which the patient had an age of 54 years. Moreover, this study stated that out of 10 patients, only one patient had a fever and headache. Interestingly our patient also reported fever and headache. In addition to it, this study by Sun and colleagues stated that all the patients had abnormal EEG7 whereas in our case, the EEG was normal.

The diagnosis of anti-amphiphysin antibody-associated meningoencephalitis is made by detecting anti-amphiphysin antibodies in the blood or CSF. However, it is a non-specific test because they can also be found in people with other autoimmune diseases, such as neuromyelitis optica spectrum disorder and transverse myelitis[8,9]. This complex presentation can make it difficult to determine whether anti-amphiphysin antibodies are the cause of the disease or just a marker. Therefore, a detailed history, thorough physical examination, and imaging studies such as computed tomography, MRI, and PET scans are crucial in the establishment of the diagnosis.

There is no specific treatment for anti-amphiphysin antibody-associated encephalitis. Treatment is usually supportive and may include medications such as corticosteroids, immunomodulatory agents, and plasmapheresis as a first line while rituximab can also be administered to those who fail to show improvement with the first-line treatment agents. Moreover, anti-seizure medications are also recommended to control seizure episodes if needed[10].

The prognosis for patients with anti-amphiphysin antibody-associated meningoencephalitis is variable. The review of available medical literature reveals that most of the patients respond well to corticosteroid or immunomodulator therapy. However, some residual symptoms persist and do not improve with the standard therapy. It is worth mentioning that our case also complained of residual symptoms.

While our case study sheds light on the fascinating link between anti-amphiphysin antibodies, meningoencephalitis, and breast cancer, it is vital to recognize its limitations. Our research is mostly observational in nature and lacks the ability to demonstrate a conclusive causal link between these parameters. Our findings, like many single-patient case studies, serve as a starting point for additional inquiry rather than conclusive confirmation of causation.

This case report has been reported in accordance with the SCARE 2020 criteria[11].

Conclusion

Anti-amphiphysin antibody-related meningoencephalitis is an intricate and difficult to diagnose paraneoplastic disease. A detailed history, thorough physical examination, laboratory, and imaging investigations are cornerstones in the establishment of diagnosis. The therapy involves the use of immunosuppressants such as high-dose corticosteroids and other immunomodulator drugs which usually show a good prognosis.

Ethical approval

NA.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

No funding

Author contribution

M.U.H. and H.A. contributed to the writing of the manuscript. M.H.G., A.S., M.U.H., M.U.M., Z.W., and L.A. contributed to writing the manuscript, editing the manuscript, and being involved in the care of the patients. All authors read and approved the final manuscript.

Conflicts of interest disclosure

There is nothing to declare.

Research registration unique identifying number (UIN)

NA

Guarantor

Lava Abdullah.

Data availability statement

The authors declared data availability statement

Provenance and peer review

Not commissioned, externally peer-reviewed

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