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Case Report

Antibodies with Clinico-Immunological Mismatch: An Emerging Conundrum

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Abstract

Introduction: The field of Neuroimmunology is expanding rapidly with the advent of newer antibodies and their phenotypes. Considering the treatability of autoimmune encephalitis asking for antibodies-panel is a common practice these days, however, its correct interpretation is of great concern. If antibody positivity, phenotype, neuroimaging is compatible with the exclusion of alternative diagnosis, the diagnosis of particular autoimmune syndrome is easily established. However, if there is any mismatch the diagnosis should be critically reviewed due to the facts that clinical spectrum of antibodies is expanding day by day, autoantibodies may be found in normal subjects, autoantibodies may also be found in non-autoimmune conditions e.g., NMDAR antibodies in CJD or MELAS and autoimmune encephalitis can still be diagnosed in the absence of autoantibodies (antibody negative autoimmune encephalitis).

Methods: Comprehensive autoimmune and paraneoplastic panels were asked in all patients meeting the diagnostic criteria for possible autoimmune encephalitis. Patients with antibody profile - phenotype mismatch were critically reviewed from clinical, radiological and immunological stand points to examine the definite contributory association of the antibody in question.

Results: Out of twenty-two cases of autoimmune/paraneoplastic encephalitis in our series so far, two cases were found to have clinico-immunological mismatch. Case 1 was anti Yo antibody positive with limbic encephalitis like presentations. Case 2 was again anti Yo antibody positive but with overlapping features of anti Yo and limbic encephalitis. Both the cases showed fair symptomatic improvement with immune modulation. Case 2 relapsed after a gap of ten months with almost the same clinical presentations but this time it tested positive for anti- ampiphysin antibody. He also tested positive for Anti TPO antibody, ANA, and anti-Centromere –B antibody.

Conclusion: Autoimmune/Paraneoplastic neurological syndromes are heterogeneous group of disorders, affecting various parts of neuraxis depending upon the antibodies. This should be kept as an important differential in all patients with subacute neurological illnesses. Atypical presentations of a particular antibody type or changing expression of antibody especially in cases of relapses or development of new symptoms, like in our case 2, though rare but are on records in literature. However, possibility of antibody of unknown significance (AUS) or chance association should also be kept. These cases reemphasize that in the face of clinico-immunological mismatch rigorous search for other possible causes should be done before labelling it as atypical presentations of the antibody in question.

Introduction

The field of neuroimmunology is expanding rapidly with the advent of newer antibodies and their phenotypes. Considering the treatability of autoimmune encephalitis asking for antibodies-panel is a common practice these days, however, its correct interpretation is of great concern. If antibody positivity, phenotype, neuroimaging is compatible with the exclusion of alternative diagnosis, the diagnosis of particular autoimmune syndrome is easily established. However, if there is any mismatch the diagnosis should be critically reviewed due to the facts that clinical spectrum of antibodies are expanding day by day, autoantibodies may be found in normal subjects, autoantibodies may also be found in non-autoimmune conditions e.g., NMDAR antibodies in Creutzfeldt-Jakob disease (CJD) or Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) and autoimmune encephalitis can still be diagnosed in the absence of autoantibodies (antibody negative autoimmune encephalitis). Here we are discussing two cases with clinico-immunological mismatch emphasising the possibilities of antibody of unknown significance (AUS) or chance association and also of changing antibody expression during follow up in such cases.

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Case Presentation

Case vignette - 1

A 56 years old male, known case of hypertension, type 2 diabetes mellitus and hypothyroidism presented with complaints of abnormal behaviour; in the form of easy irritability, jitteriness; poor interaction with people around; forgetfulness for the recent events; disturbed sleep and off and on low grade fever for twenty days. On admission, GCS was E4M6V4, Pupils were bilaterally 3 mm and reacting to light, moving all four limbs equally, global hyporeflexia, plantars were bilaterally flexor and no meningeal signs. On the day of admission patient had one episode of generalized tonic clonic seizure followed by altered sensorium. MRI brain showed signal changes in bilateral mesial temporal lobes (Figure 1). CSF study revealed cells 210

with 65% lymphocytes, protein- 179 mg/dl, sugar- 103 mg/dl with corresponding blood glucose 188, ADA 11.5, no organism seen on gram staining, no AFB seen on Z N stain, CSF culture was negative. EEG revealed abnormal drowsy record showing brief paroxysm of generalized symmetrical and bi-synchromous biphasic and triphasic wave morphology. Based on the above observations, a possibility of sub-acute encephalitis syndrome was thought of, with possible aetiologies being infective and autoimmune/paraneoplastic disorders. CSF-pan-neurotropic viral panel, CSF-TB-PCR, and autoimmune-paraneoplastic panels were sent. As the patient's condition was further deteriorating, he was intubated and put on mechanical ventilator and initiated on plasmapheresis. He showed substantial improvement after second cycle of plasmapheresis. He received total of four cycles with fair functional improvement. In the meantime, report came positive for anti Yo antibody, other reports being negative. As the clinical presentations did not match the antibody detected i.e., anti Yo, the diagnosis of Autoimmune/paraneoplastic encephalitis with anti Yo antibody positive was kept. During hospital stay patient also developed flaccid quadriparesis. Nerve conduction study showed pre-dominantly axonal motor polyradiculoneuropathy suggestive of critical illness neuropathy (CINM) which was managed with low dose insulin infusion, micronutrient supplementation and physiotherapy. Patient also had multiple episodes of infection during stay, viz. Catheter tip C/S showed klebsiella pneumonia, Urine C/S showed myrmidons, Blood C/S showed klebsiella pneumonia, for which the patient was managed according to sensitivity profile along with other supportive measures. He underwent Tracheostomy owing to the need for prolonged ventilation. He was evaluated for occult malignancy with CT-chest, CT-abdomen, USG-salivary gland. His vasculitis markers were negative. Whole body FDG-CTPET was also planned but could not be done due to nonavailability of test at our centre. Gradually patient improved functionally, weaned off from ventilator, tracheostomy tube removed and patient mobilized with support (Figure 1). At the time of discharge, patient was conscious, alert, following commands, speech hypophonic (due possibly to prolonged tracheostomy), can sit unsupported, stand and walk with one person's support and was continent of stool and urine.

Case vignette -2

A 58-year-old male presented with complaints of acute onset imbalance, clumsiness mild slurring of speech followed by confusion and jitteriness for 8 days. There was no history of recent febrile illness, seizure or loss of consciousness. He had past medical history of possible Paraneoplastic/Autoimmune encephalitis [AntiYo +ve, Anti TPO +ve, ANA -+ve, Centromere –B +ve] ten months back which improved with immune modulation therapy. He had other comorbidities viz. Hypertension, Hypothyroidism and Dyslipidemia. On examination he was Conscious, alert, disoriented to time and place. Speech was Normal, extra ocular movements were full and normal, Pupils were bilaterally 2 mm and reacting to light, no facial asymmetry, Palatal arching normal and Uvula central in position. Bulk and nutrition were average, tone normal, power was 5/5 in all four limbs, deep tendon reflexes were normal, Plantar were bilaterally flexor, sensory- could not be tested properly, Romberg's test was negative, heel-knee-shin test was positive, ataxic gait, no meningeal sign and other systemic examinations were unremarkable. MRI brain was non-contributory, CSF showed cell count 17/cumm (95% lymphocyte, 5% neutrophil), Protein 91 mg/dl, Sugar 110 mg/dl. Possibility of relapse of paraneoplastic/ autoimmune encephalitis was kept. Intravenous infusion of Methylprednisolone (1000 mg) given for three days followed by weight adjusted, IVIG therapy. In the meantime, his autoimmune and paraneoplastic panel results came, which showed anti Amphiphysin antibody positive, anti TPO was high (75.85). Patient improved remarkably on the day 4 of IVIG therapy. At the time of discharge, patient was conscious, alert, oriented and hemodynamically stable. Whole body CT – PET was done in follow up which did not show any significant hyper or hypo-metabolic focus.

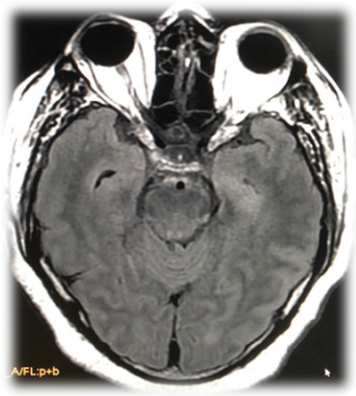

Figure 1: Axial T2FLAIR image of patient with ati Yo positive antibody showing bilateral mesial temporal lobe hyperintensities.

Discussion

Conglomeration of symptoms like memory impairment, behavioural changes and seizure (usually complex partial seizure) along with unilateral or bilateral mesial temporal hyperintensities especially on T2 FLAIR sequence are the usual manifestations of limbic encephalitis [1,2]. Limbic encephalitis can occur in both paraneoplastic and nonparaneoplastic settings. Commonly associated cancers are SCLC, testicular germ-cell tumors, teratoma (usually of the ovary), thymoma, and Hodgkin lymphoma [2]. Anti Hu, Ma2, CV2/CRMP5 are the main causes of limbic and brainstem encephalitis [2]. Limbic encephalitis may also be associated with antibodies to AMPA receptor, GABA(B) receptor, NMDA receptor, LGI1 or mGluR5 [2]. A comprehensive antibody panel from CSF and serum along with MRI of brain in a proper clinical setting is required for the diagnosis [3]. CT-PETscan of whole body helps in picking up the occult tumors. Treatment is usually immunotherapy (IVIG, plasma exchange and other immunomodulators) and tumor directed therapy. Prognosis depends upon the associated antibodies and tumor types. Paraneoplastic cerebellar degeneration (PCD) is characterized by the rapid development of severe pancerebellar dysfunction. Usual clinical features are truncal and appendicular ataxia, dysarthria, and downbeat nystagmus. Anti-Yo is the most frequent and well-characterized antibody associated with PCD [4]. The antibody is usually associated with breast or gynecologictumors. Anti-Yo antibodies, however, have been identified in a few male patients with PCD and cancer of the salivary gland, lung, and esophagus. Response to treatment is usually not good in PCD due to early neuronal loss [5]. Other antibodies associated with PCD are anti Ri, anti Tr, anti Ma, anti Hu, anti CV2/CRMP5, anti VGCC etc. Case vignette 1 was distinct owing to association of anti Yo antibodies with limbic encephalitis like presentation, that too in male and response to immune therapy being reasonably good unlike usual PCD cases. Patients with encephalitis may recover, completely or partially, and then experience worsening symptoms. In autoimmune encephalitis, relapse tends to

follow a similar clinical course to the initial attack. In anti-NMDAR encephalitis, these relapses tend to be milder than the initial attack, in other types of autoimmune encephalitis, the risk of relapse is less clearly established [6]. Relapsed patients are usually treated with second-line therapies, possibly after first line therapies. These patients may be treated for longer periods of time with second line therapy, especially rituximab, but the optimal duration of treatment has not been established. Anti-Amphiphysin targets an intracellular protein important for recycling synaptic vesicles. The antibodies are usually associated with breast cancer and manifest as stiff person spectrum disorder; however, these are not specific for one type of tumour or one neurological syndrome and can be associated with many neural and nonneural antibodies. The simultaneous association of several antibodies in some patients suggests multimodal autoantibody production [7]. Case vignette 2 presented with relapse of symptoms pertaining to gait, coordination, and cognitive issues after roughly 10 months of the initial symptoms. The striking point was the fact that earlier it was associated with anti Yo antibody and this time with anti amphiphysin antibody, however, symptomatology was a little odd for both the phenotypes. Whether this is a chance association or more than what meet the eyes needs to be delved into. There have been a few cases where NMDAR encephalitis was associated with optic neuritis and/or transverse myelitis, wherein NMDAR antibodies was thought to be directly pathogenic to this or may be triggering production of other antibody like aquaporin 4 [8]. Our patient also tested positive for anti-centromere B antibodies and ANA, though there were no symptoms or signs commensurating with CREST or scleroderma neither with SLE. There are reports suggesting that a positive antinuclear antibody test does not always indicate the presence of a connective tissue disease, but the presence of anticentromere antibody without systemic sclerosis or CREST often indicates the presence of another sometimes serious underlying rheumatic or connective tissue disease [9]. There are reports of patients with systemic lupus erythematous who later develop anti-NMDAR encephalitis or limbic encephalitis. This further raises a question as to whether these immune dysregulation disorders like SLE predispose a patient to the development of further autoimmune phenomena like AE [10,11]. The issue which made us curious was distinctive shifting antigenic expression in our case and association with other auto-antibodies; which might require further detailed study in similar patients before been written off as a chance association.

Conclusion

Paraneoplastic neurological syndromes are heterogeneous group of disorders, affecting various parts of neuraxis depending upon the tumour types, which are increasingly being reported with the advent of tools and techniques to recognise respective onconeuronal antibodies and occult malignancy. This should be kept as an important differential in all patients, in their fourth decade onwards, with subacute neurological illnesses. Atypical presentations of a particular antibody type or changing expression of antibody especially in cases of relapses or development of new symptoms, like in our case 2, though rare but are on records in literature; however, possibility of antibody of unknown significance (AUS) or chance association should also be kept. These cases reemphasize that in the face of clinico-immunological mismatch rigorous search for other possible causes should be done before labelling it as atypical presentations of the antibody in question.

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