Coexistence of IgLON5-IgG and SOX1-IgG in a Patient with Progressive Brainstem Dysfunction

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Abstract

Purpose: The coexistence of IgLON5-IgG and SOX1-IgG is rare. Previous reports have shown that patients with IgLON5-IgG spectrum disease present with sleep disorders, bulbar involvement, and autonomic abnormality, while SOX1-IgG positive patients present with peripheral nervous system symptoms such as the Lambert–Eaton Myasthenic Syndrome (LEMS).

Case Report: We report a patient who presented with progressive ophthalmoplegia, ptosis, oropharyngeal dysphagia, gait instability, and sleep disorders. The paraneoplastic antibody screening tested double-positive for IgLON5-IgG and SOX1-IgG. However, there was no clinical sign of LEMS in this patient. After extensive cancer screening, only lung nodules with hilar adenopathy were noted.

Conclusion: The coexistence of IgLON5-IgG with onconeuronal SOX1-IgG would suggest an underlying immune-mediated paraneoplastic process rather than secondary autoimmunity because of neurodegeneration. This is the first IgLON5-IgG case reported in Thailand, with a case of double-positive IgLON5-IgG and SOX1-IgG as well.

Keyword: IgLON5-IgG, SOX1-IgG, Paraneoplastic process, case report

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INTRODUCTION

IgLON5 belongs to the IgLON family which was considered a part of neuronal cell adhesion molecule with unclear function. However, IgLON5 has been in focus because of recent reports of cases that developed antibodies targeted to IgLON5 molecules[1,2]. Anti-IgLON5 disease is first reported from a case series of eight patients in 2014 who presented with sleep disorders, bulbar involvement, and autonomic abnormality[3]. The increase of IgG4 subclass antibody leads to neuronal surface protein IgLON5 internalization and abnormal

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accumulation of hyperphosphorylated tau in the hypothalamus, tegmentum, periaqueductal gray matter, and other parts of the brainstem. Regarding immune-mediated disease, immunoglobulins, immunosuppressive drugs, and plasma exchange become the chosen treatment with variable outcomes.

SOX1-IgG is one type of anti-glial nuclear antibody (AGNA) and is found in significant association with small cell lung cancer (SCLC) and Lambert-Eaton Myasthenic Syndrome (LEMS). The SOX1 protein is a part of the SOXB1 group which belongs to the SRY-like high mobility group superfamily of developmental transcription factors. The SOX1 along with SOX2 and SOX3 protein presumptive function is mainly in neural progenitor cell differentiation and some of them are associated with respiratory epithelial differentiation. Many investigators focus on SOX1-IgG as a possible immunologic target to detect SCLC[4].

No case was found in the literature of the coexistence of IgLON5-IgG and SOX1-IgG. This case report will provide an illustrated case with a discussion.

CASE REPORT

A 65-year-old Thai right-handed man visited at neurology clinic at Maharaj Nakorn Chiang Mai Hospital with diplopia, insomnia, and slurred speech for a month. The patient had hypertension, type 2 diabetes mellitus, old cerebrovascular disease, and chronic hepatitis B infection, and received aspirin, statin, oral hypoglycemic, and antihypertensive drugs. He had a limited bilateral lateral rectus (90% of normal function) without pain on eye movement. Dysarthria was also noted. Other examinations appeared unremarkable. His CSF analysis showed no pleocytosis, with normal protein, and sugar levels. The MRI of his brain revealed age-related brain atrophy.

Six months later, he had progressive diplopia and ophthalmoplegia. The right eye showed 20% of lateral rectus (LR), 20% of medial rectus (MR), 50% of superior rectus (SR), 100% of inferior oblique (IO), and 50% of superior oblique (SO). The left one showed 40% of LR, 20% of MR, 50% of SR, 100% of IO, and 80% of SO. A repeat MRI of the brain was performed and was still unchanged. Gait instability with mild motor weakness was noted (MRC grade 4/5 all). At that time, the serum for paraneoplastic antibody was evaluated by immunohistochemistry assay using a frozen composite section of mouse cerebrum/cerebellum, gut, and kidney tissues. Bound IgG was detected by applying Alexa Flour-conjugated goat-IgG reactive with all human IgG subclasses. The pattern of more prominent in cerebellar staining than in the hippocampus and also renal glomeruli and gut smooth muscle staining was compatible with IgLON5-IgG reactivity (Figure 1). The specificity of

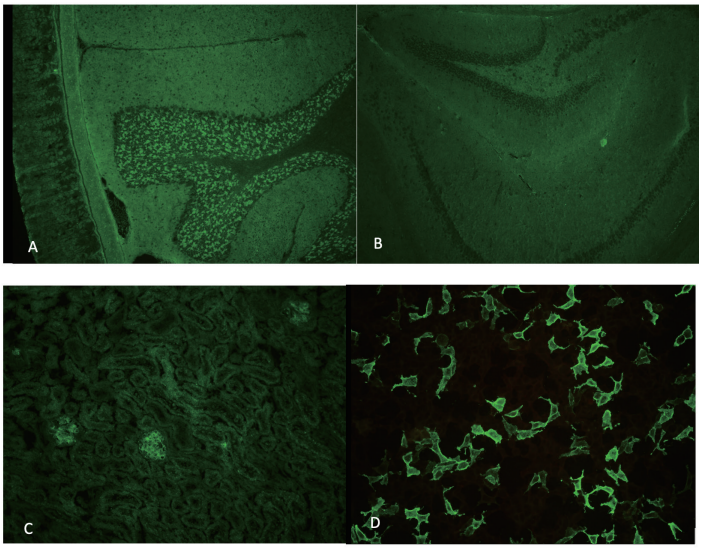

Fig. 1. Immunoreactivity of IgLON5-IgG on mouse brain section showed A: prominent staining in the molecular layer (ML) and granular layer (GL) of the cerebellum. B: less immunostaining in the hippocampus. C: prominent staining in kidney glomeruli. D. Immunostaining on HEK 293 transfected with IgLON5 complementary DNA

IgLON5-IgG was also confirmed with a cell-based assay on human embryonic kidney 293 cells transfected with the IgLON5 complementary DNA (Euroimmun). The serum was also tested by EUROLINE@ (Euroimmun) and yielded seropositive for SOX1-IgG. CT chest showed a 3.9-mm nodule and 5.7-mm nodule in the posterior segment of the right lower lobe with multiple calcified bilateral hilar and mediastinal lymph nodes. Steroids and azathioprine were given to the patient.

Seven months later, the patient had dysphagia and episodes of frequent choking. Endoscopic gastroduodenoscopy was compatible with pharyngoesophageal reflux. Gastrointestinal follow-through showed normal swallowing function. The fiber optic laryngoscopy was unremarkable. Oropharyngeal dysphagia was diagnosed. At that time, his wife reported that he had been snoring, witnessed apnea, and sleep talking. He received split-night polysomnography. Severe obstructive sleep apnea was diagnosed with an apnea-hypopnea index (AHI) of 88%. Partial response was observed after CPAP was used. His Montreal cognitive assessment test (MoCA) was 26/30. Eighteen months later, a CT of his chest and abdomen reported that the nodules were unchanged with the suspected benign nodule. Two years after the first visit, he had a severe degree of ophthalmoplegia with only 10% of IR and SO bilaterally while the others appeared completely limited function. He became wheelchair-bound and died from a pulmonary infection one month later.

DISCUSSION

We reported the case with chronic and severely progressive ophthalmoplegia, dysarthria, ptosis, gait disturbance, dysphagia, insomnia, and severe obstructive sleep apnea. All these features were compatible with brainstem dysfunction. IgLON5-IgG and SOX1-IgG were detected. Extensive malignancy screening showed pulmonary nodule with hilar adenopathy unchanged at the time of follow-up.

This patient's clinical symptoms were compatible with "classic" IgLON5-IgG autoimmunity disorder. Age-related brain atrophy with another prominent lesion, no CSF pleocytosis, and no increased CSF protein was compatible with the previous case series. Azathioprine and steroids were given to this patient with little response.

The coexistence of IgLON5-IgG and SOX1-IgG is very rare. No case report was identified of a double-positive case. IgLON5-IgG spectrum disease mostly presents with central nervous system symptoms especially brainstem dysfunction while SOX1-IgG patients are likely to have peripheral nervous system symptoms (mostly were LEMS) which was not found in this patient. However, the presence of onconeuronal antibodies would predict cancer rather than a specific neurological syndrome. This case could not prove the malignancy by pathological tissue except for the pulmonary nodules by imaging. But the limited form of lung cancer could not be ruled out even though the lung nodules and mediastinal nodes had not changed eighteen months later. The tumor suppression ability of the cytotoxic T cell which also caused the paraneoplastic neurological disease may explain this finding. In pathologically established CJD cases, autoantibodies against the N-methyl-D-aspartate (NMDA) receptor or the voltage-gated potassium channel (VGKC) complex have been identified in serum but not in CSF[5]. In another study, anti-NMDAR was found to be co-existing with anti-aquaporin 4 (AQP4) or anti-myelin oligodendrocyte glycoprotein (MOG)[6,7]. The release of antigens by neuronal cell death as a result of the degenerative process could explain secondary autoimmunity from neurodegeneration. These antigens may activate the immune system production of antibodies that target cell surface antigens. Contrarily, SOX1-IgG targets the antigen at the nucleus, not the cell surface epitope. We considered that the positive findings of coexisting IgLON5-IgG with SOX1-IgG would suggest the paraneoplastic process which may support the underlying immune-mediated process of primary autoimmunity rather than the secondary immunity due to neurodegeneration.

Until now, there was a scarcity of information on prognosis and management in individuals with double-positive antibodies. In a published study, patients with positive NMDA receptor-IgG with anti-AQP4 or anti-MOG antibodies may have atypical and overlapping symptoms for both disorders, making diagnosis difficult.6 Compared to our case, positive IgLON5-IgG and SOX1-IgG may share both classic symptoms of IgLON5-IgG and SOX1-IgG-related diseases. Double-positive cases might carry poorer outcomes. However, further studies are

required to explain the association.

From our autoimmune screening laboratory database 2010-2017 comprising approximately 13,000 samples, there were five positive samples for SOX1-IgG or anti-glail nuclear antibody (AGNA). The first case is a 77-year-old man who presented necrotizing myopathy. The second case was a 66-year-old man who presented with polyneuropathy. The third case involved a 52-year-old lady who had sensory ataxia. The fourth case is a 79-year-old man suffering from encephalopathy. The fifth case is a 67-year-old woman who had cerebellar ataxia. Only one of five cases (the third case) had concomitant tissue-confirmed SCLC. In contrast to earlier published studies, the symptoms of individuals in our registry were not limited to LEMS. However, the data on underlying tumors in each case was limited because our institute is a referral center for mainly laboratory investigations. Tissue-proven investigation, on the other hand, is invasive and not commonly available.

The presence of the SOX1-IgG in our case could be a subsequent autoantibody following glial cell death, or it could be co-existing, as patients with autoimmune disease frequently have several antibodies. Coexisting paraneoplastic antibodies are not uncommonly encountered and help to predict cancer[8]. Even though the presence of co-existing antibodies may not be clinically significant, it is suggested that tumor-negative individuals with onconeuronal antibodies undergo serial tumor surveillance for at least two to five years[9]. However, further studies and case series were needed to evaluate this association.

CONCLUSION

The coexistence of IgLON5-IgG and SOX1-IgG can occur as they are considered autoimmune diseases. However, it is very rare. The appropriate tumor screening regarding age, sex, and other risk factors is suggested. Further studies are needed to evaluate this condition.

Learning points

IgLON5-IgG is a neuronal surface protein antibody and is usually associated with progressive ophthalmoplegia, ptosis, oropharyngeal dysphagia, gait instability, and sleep disorders.

Even though IgLON5-IgG-related disease is rarely associated with the paraneoplastic process, coexisting paraneoplastic antibodies are not uncommonly encountered and help to predict cancer.

When the appropriate tumor screening regarding age shows unremarkable study, further extensive tumor screening must be concerned.

Data availability

According to an ethical issue, the data can be disclosed upon appropriate request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical issue

This study was reviewed by the Research Ethics Committee of Faculty of Medicine, Chiang Mai University. STUDY CODE: MED-2564-08690 Research ID: 8690. The patient's informed consent was acquired.

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