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Autoimmune glial fibrillary acidic protein myelitis with laryngeal cancer: a case report and literature review

DE-MEI JIA[1], RUI-QIONG BA[2], XIA ZHOU[3], SHAN-LAN YANG[4], SHU-JI GAO[5], MING-WEI LIU[6]

[1]Physical Examination Center, The Affiliated Hospital of Yunnan University, Yunnan, China
[2]Department of Neurology, First People's Hospital of Qujing City, Qujing, China
[3]Department of Human Resources, Dali Bai Autonomous Prefecture People's Hospital, Dali Bai, China
[4]Department of Oncology, Dali Bai Autonomous Prefecture People's Hospital, Dali Bai, China
[5]Department of Emergency, The First Affiliated Hospital of Kunming Medical University, Kunming, China
[6]Department of Emergency, Dali Bai Autonomous Prefecture People's Hospital, Dali Bai, China

Abstract

Glial fibrillary acidic protein astrocytopathy (GFAP-A) is a recently recognized autoimmune disorder affecting the central nervous system, with predominant involvement of the brain, meninges, spinal cord, and optic nerves. Although frequently associated with neoplasms, its co-occurrence with laryngeal carcinoma remains undocumented. We describe a 70-year-old male patient presenting with progressive lower limb weakness and bowel/bladder dysfunction evolving over two weeks. Six months earlier, he had been diagnosed with laryngeal squamous cell carcinoma, and underwent surgical resection followed by adjuvant radiotherapy and chemotherapy. Cerebrospinal fluid (CSF) analysis demonstrated pleocytosis (67×10^6/l) with 92% mononuclear predominance. Critically, GFAP antibody testing of the cerebrospinal fluid confirmed positivity. This patient has been diagnosed with autoimmune GFAP myelitis with laryngeal cancer. Immunotherapy comprised intravenous methylprednisolone (initial 480 mg/day), tapered to 60 mg, followed by biweekly 5 mg reductions. Concurrently, neurotrophic therapy was administered. After immunomodulation, the patient demonstrated marked resolution of chest tightness and bowel/bladder dysfunction. Urinary catheter removal coincided with improved lower limb strength (bilateral IV+), allowing independent ambulation at reduced velocity. Subsequently, the patient was discharged. In conclusion, following laryngeal cancer surgery, new-onset lower limb weakness with bowel/bladder dysfunction warrants consideration of autoimmune GFAP myelitis alongside spinal metastases in differential diagnosis. Prompt neuroaxis MRI (cranial/cervical/lumbar) and cerebrospinal fluid GFAP antibody testing are essential to mitigate diagnostic delays.

Key words: *case report, diagnosis, glial fibrillary acidic protein myelitis, laryngeal cancer, literature review.*

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Introduction

Glial fibrillary acidic protein astrocytopathy (GFAP-A) is an autoimmune-mediated inflammatory disorder predominantly affecting the brain, meninges, spinal cord, and optic nerves. Core clinical features comprise fever, headache, encephalopathy, myelitis, and visual impairment [1, 2]. This antibody-mediated condition affects all age groups, with median onset at 44 years. No gender predilection has been established. Approximately 29% of patients report prodromal upper respiratory symptoms [1]. Subacute headache constitutes the most common presentation [2], while additional features encompass papilledema, peripheral neuropathy, dyskinesia, cerebellar ataxia, autonomic dysfunction, psychiatric symptoms, and seizures [1]. Hyponatremia affects approximately 57% of inpatients [1], and thromboembolism occurs in 21% [2].

Approximately 34-38% of GFAP-immunoglobulin (Ig) G seropositive patients develop concurrent neoplasms. GFAP-IgG positivity is associated with diverse malignancies – including teratomas, prostate/gastroesophageal adenocarcinomas, myeloma, melanoma, colon carcinoids, and parotid pleomorphic adenomas – occurring pre-/post-disease onset [3]. Notably, no published reports have associated GFAP-IgG seropositivity with laryngeal carcinoma. While cerebrospinal fluid GFAP-IgG detection remains

Correspondence: Prof. Ming-Wei Liu, Department of Emergency, Dali Bai Autonomous Prefecture People's Hospital, Dali Bai, China, e-mail: lmw2004210@163.com
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a diagnostic cornerstone, clinical differentiation poses substantial challenges. Nonspecific symptomatology mimics other CNS disorders, confounding differentiation and increasing the risk of diagnostic errors. We report a GFAP myelitis case comorbid with laryngeal squamous cell carcinoma at the Department of Neurology, First Affiliated Hospital of Kunming Medical University, aiming to improve diagnostic vigilance and prevent diagnostic pitfalls.

Case study

A 70-year-old male farmer presented with progressive lower limb weakness and sphincter dysfunction evolving over two weeks. On May 19, 2021, he developed progressive bilateral lower limb weakness (right > left), culminating in ambulatory impairment. Associated symptoms included chest tightness and incontinence without remission. Notably absent were visual disturbances, limb paresthesia, fever, rhinorrhea, or diarrhea. Initial oncology evaluation prompted symptomatic management: neurotrophic agents and urinary catheterization provided minimal relief. On June 5, thoracolumbar MRI (with/without contrast) demonstrated T1-T12 signal abnormalities, suggesting inflammatory changes, metastatic lesions, or alternative etiologies. The patient was transferred to the Department of Neurology at the First Affiliated Hospital of Kunming Medical University for specialized care.

In November 2020, the patient was diagnosed with laryngeal squamous cell carcinoma at the Affiliated Hospital of Zhejiang University, Hangzhou, and subsequently underwent surgical resection. Postoperative management consisted of radiotherapy and chemotherapy. The patient had no reported history of hypertension or diabetes.

The patient's general condition was fair. Vital signs were stable. Cardiopulmonary and abdominal examinations showed no abnormalities. No lower limb edema was noted. An oral ventilation tube was placed in the pharynx, and a urinary catheter was inserted. Neurological examination showed clear consciousness, with a Glasgow Coma Scale (GCS) score of 15 (eye response: 4, verbal response: 5, motor response: 6). Higher cortical functions and cranial nerves were found to be intact. Muscle strength was graded IV in both proximal and distal segments of the right lower limb, IV in the left lower limb, and V in both upper limbs. Muscle tone was within normal limits. Tendon reflexes demonstrated hyperreflexia in the right lower limb (knee and Achilles reflexes: +++), whereas reflexes in other limbs were moderately brisk (++). Pathological reflexes were not elicited. Sensory examination showed reduced pinprick and touch sensation below the left T4 dermatome, while pinprick, touch, position, and vibration senses were normal in the upper limbs. Limb and trunk coordination was intact, and autonomic functions were normal. The modified Rankin Scale (mRS) score was 3.

The erythrocyte sedimentation rate (ESR) was 34 mm/h. C-reactive protein (CRP) was 9.35 pg/ml. Antinuclear antibodies (ANA, nucleolar type, ANAHX6) were positive, with a titer of 1 : 100. The rheumatoid factor (RF)-IgM level was 133.68 RU/ml. Routine hematology tests, hepatic and renal function evaluations, and tests for anti-neutrophil cytoplasmic antibodies (ANCA), Sjogren's syndrome antigen A (SSA), Sjogren's syndrome antigen B (SSB), and anticardiolipin antibodies (ACA) were all negative. Tumor marker analysis revealed a CA125 level of 42.8 U/ml and CYFRA21-1 level of 3.5 ng/ml. Thyroid function tests showed that the thyroid stimulating hormone (TSH) level was 10.53 μIU/ml, antithyroid microsomal antibody level was 132.90%, and thyroglobulin antibody level was 459.70%. Lumbar puncture revealed that cerebrospinal fluid pressure was 118 mmH_2O. The white blood cell count was 67 × 10^6/l, consisting of 92% mononuclear cells and 8% multinuclear cells. Cerebrospinal fluid immunoglobulin levels were 61.90 mg/l for IgG and 7.36 mg/l for IgA. Biochemical analysis showed that total protein was 0.510 g/l. GFAP antibody testing of cerebrospinal fluid by cell-based assay (CBA) showed a positive result at a titer of 1 : 32 (Fig. 1).

An MR scan of the neck with and without contrast showed post-subtotal laryngectomy changes, characterized by marked thickening of the laryngeal soft tissue compared to previous imaging (Fig. 2). Brain and optic nerve MR scans with and without contrast identified abnormal areas in the left frontal and temporal lobes, as well as bilateral cerebellar hemispheres, with softening foci and adjacent gliosis (Fig. 3). On June 5, thoracolumbar spinal cord MR imaging with and without contrast demonstrated signal abnormalities at T1-12, suggesting an inflammatory process (Fig. 4).

Based on clinical symptoms, laboratory findings, head/neck/chest/lumbar spine MRI, and positive cerebrospinal fluid GFAP antibodies, the patient was diagnosed with autoimmune GFAP myelitis after laryngeal squamous cell carcinoma surgery. During hospitalization, an initial methylprednisolone dose of 480 mg was administered, then tapered to 60 mg with 5 mg reductions every two weeks. After two weeks of treatment, symptoms including chest tightness and genitourinary/bowel dysfunction improved. The urinary catheter was removed; bilateral lower limb muscle strength improved to IV+; and the patient could walk unassisted at a slow pace, which prompted hospital discharge.

After discharge, the patient showed continuous symptomatic improvement during gradual tapering of oral corticosteroids, combined with neurotrophic therapy. Limb pain improved, and tapering of oral corticosteroids continued. At six-month follow-up, evaluations showed significant improvement, with decreased limb numbness, pain, and weakness, allowing independent walking and self-care. The patient was advised of the recurrence potential

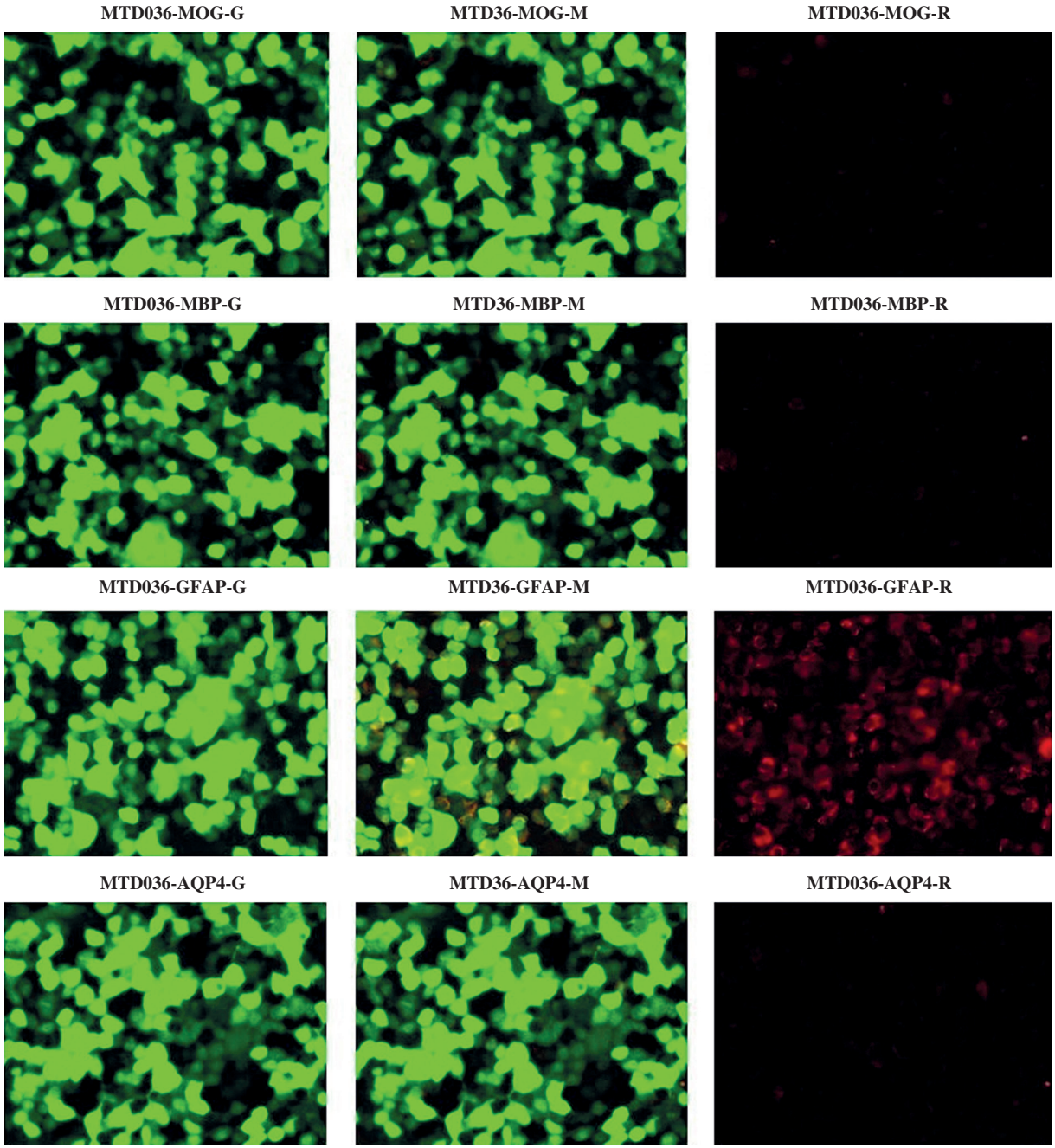

Fig. 1. Cerebrospinal fluid analysis by cell-based assay (CBA) detected anti-aquaporin 4 (AQP4) antibody, anti-myelin oligodendrocyte glycoprotein (MOG) antibody, anti-glial fibrillary acidic protein (GFAP) antibody, and anti-myelin basic protein (MBP) antibody

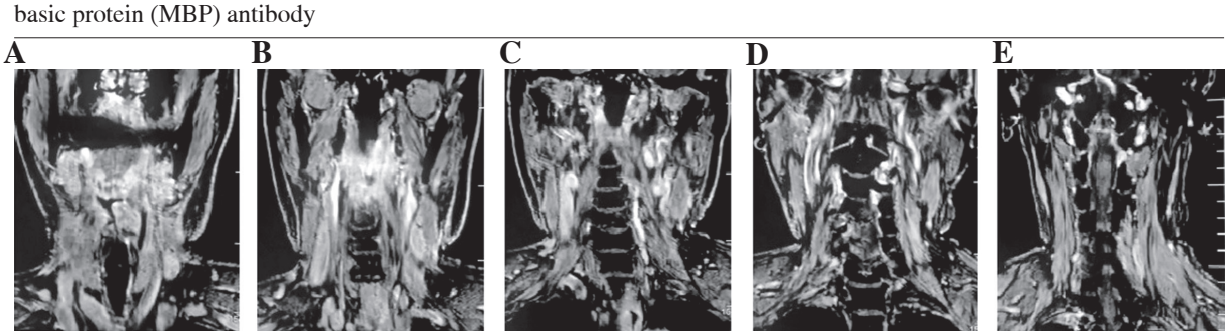

Fig. 2. Neck MRI without contrast (**A-E**) showed post-subtotal laryngectomy changes, with marked thickening of the laryngeal soft tissue

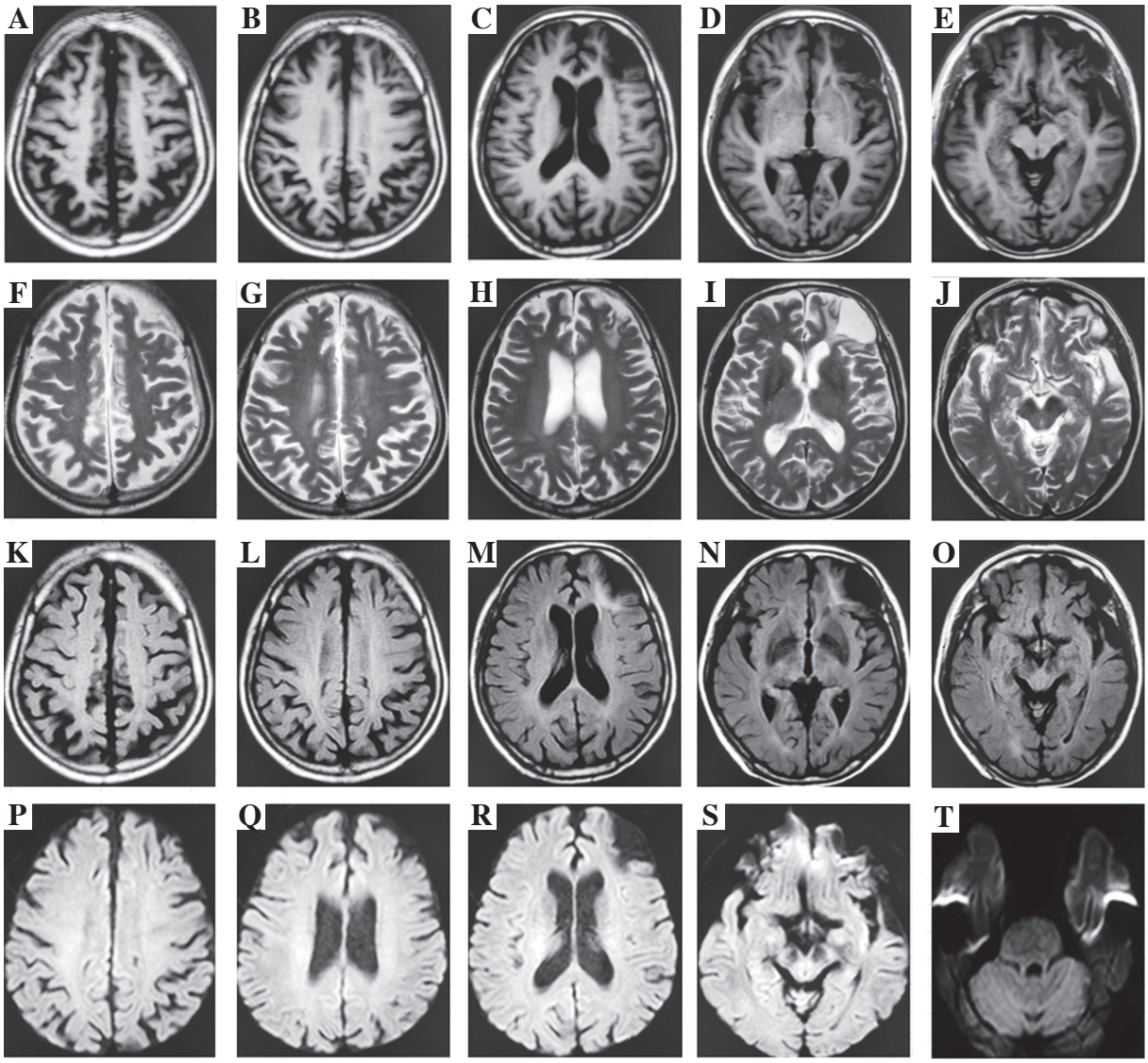

Fig. 3. Non-contrast head MRI revealed abnormal signals in the left frontal and temporal lobes, as well as bilateral cerebellar hemispheres, with softening foci and adjacent gliosis. Imaging modalities included T1 (**A-E**), T2 (**F-J**), FLAIR (**K-O**), and DWI (**P-T**)

and instructed to promptly seek medical care if symptoms recurred.

Discussion

The GFAP antibody was first identified in 2016 by the Neuroimmunology Laboratory, Mayo Clinic [3]. GFAP, an intermediate filament protein primarily localized in astrocyte cytoplasm, is crucial for maintaining astrocyte structure and function. In addition to its structural role, GFAP is involved in processes including cell adhesion, neuronal stabilization, and brain myelination [4]. Current evidence indicates that GFAP astrocytopathy is mediated by cytotoxic T cell-driven immune responses, with GFAP-IgG serving as a diagnostic biomarker [5]. The underlying mechanisms remain unclear, but viral infections and tumors are hypothesized as potential triggers, meriting further investigation [3, 6]. GFAP-A often co-occurs with other autoimmune disorders, particularly rheumatic diseases, endocrine disorders, or neuromyelitis optica spectrum disorders (NMOSD) [3]. Overlapping autoantibodies are seen in approximately 40% of cases, with notable associations in teratoma patients, where GFAP-IgG often coexists with NMDA receptor (NMDAR)-IgG, AQP4-IgG, MOG-IgG, and MBP-IgG [3]. In this case, AQP4 antibody, MOG antibody, and MBP antibody tests were negative, indicat-

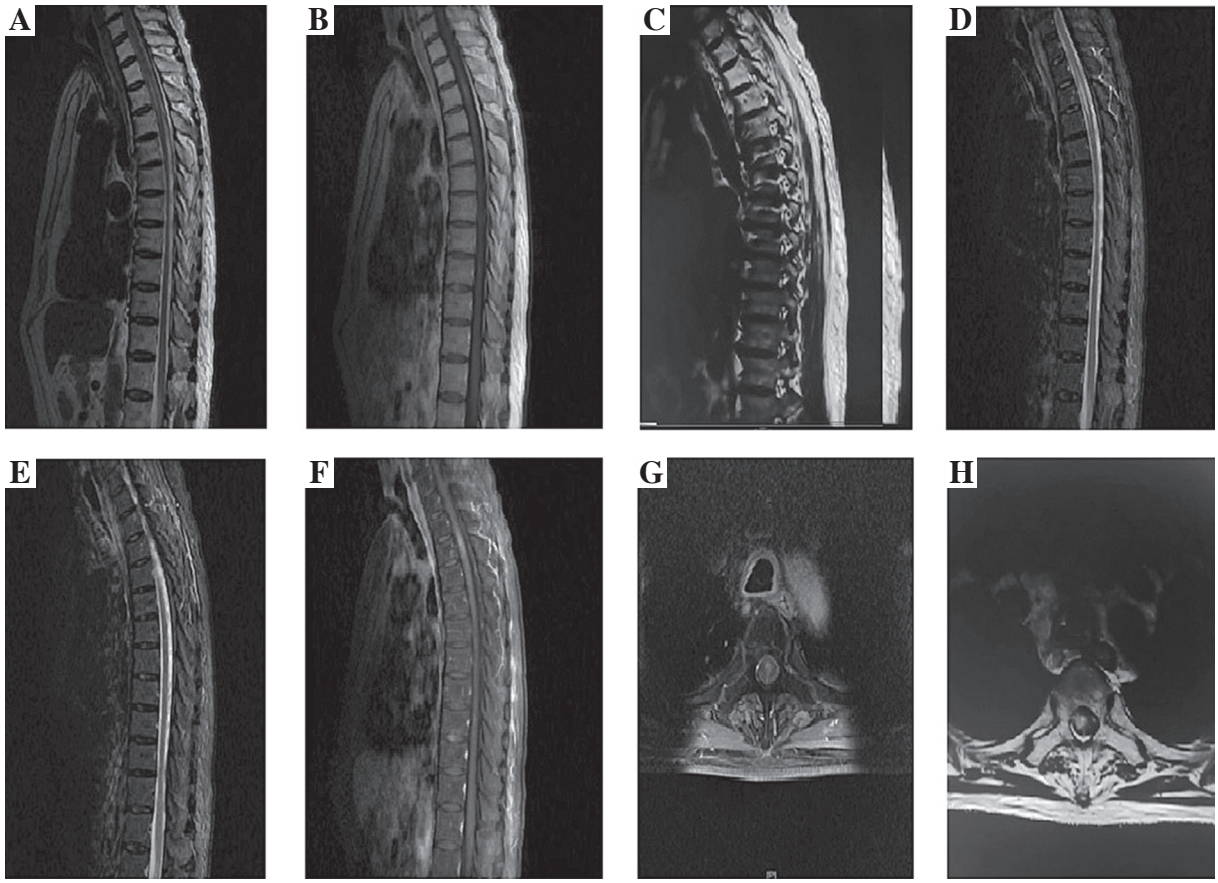

Fig. 4. Thoracolumbar spinal cord MRI showed heterogeneous signals at T1-T12, with scattered patchy foci of slightly hyperintense T2 and isointense T1 signals. Post-contrast imaging showed irregular enhancement, most prominent at T2-T4. Axial images confirmed central gray matter involvement. Modalities included T1 (**A**), T2 (**B, C**), contrast-enhanced images (**D-F**), and axial scans (**G, H**)

ing that GFAP-A did not co-occur with these antibodies or develop an overlap syndrome. Non-neuronal antibodies, including ANA, SSA/SSB, and anti-dsDNA antibodies, are commonly detected in these cases [3]. Patients with anti-GFAP antibody positivity often have other nervous system autoantibodies. However, Lin *et al*. [7] reported no significant differences in clinical features between patients with and without additional autoantibodies, except for age at onset. Studies have shown that 34% of patients had tumors, with 66% developing them within two years of neurological symptom onset [3]. Common tumor types include ovarian teratoma, adenocarcinoma (breast, lung, ovarian, endometrial, esophageal, renal), squamous cell carcinoma (head and neck), pleomorphic parotid tumor, thymoma, glioma, multiple myeloma, small cell lung cancer, and carcinoid [8]. In addition, 14% (3/21) of patients in the cohort had a history of tumors [3]. Current evidence suggests that tumors trigger autoimmune GFAP astrocytopathy through abnormal expression of GFAP-structural homologs – e.g., sex-determining region Y-box 2 (SOX2) and crystallin alpha B (CRYAB) – in tumor cells, inducing the immune system to produce cross-reactive antibodies against astrocytic GFAP [9]. GFAP-IgG was detected in the serum of ovarian teratoma patients [9]. Following tumor resection, antibody titers decreased and neurological symptoms improved [9]. The tumor microenvironment releases damage-associated molecular patterns (DAMPs), activates dendritic cells, expands self-antigen (GFAP) presentation, and promotes polyclonal T/B cell activation [10]. Tumors secrete pro-inflammatory cytokines (e.g., IL-6, IL-17), disrupting blood-brain barrier tight junctions (occludin degradation) and enhancing GFAP antibody infiltration into the central nervous system [11]. The present case concerns a patient with a history of laryngeal squamous cell carcinoma, which was surgically resected one year before disease onset. During hospitalization, blood tests showed multiple positive antibodies, including thyroid autoantibodies, ANA, and RF, indicating tumor-induced systemic multi-system immune dysregulation.

GFAP-A mainly affects individuals over 40 years old, typically presenting with acute or subacute onset. Core clinical manifestations include fever, headache, encephalopathy, myelitis, and visual disturbances. A subset of patients may present with ataxia, autonomic dysfunction, or peripheral neuropathy [3]. Pathologically, common sites of involvement include the subcortical white matter, hypothalamus, basal ganglia, cerebellum, brainstem, and spinal cord [12]. Characteristic MRI findings show linear gadolinium enhancement along periventricular white matter vessels, which are oriented perpendicularly to the ventricles on contrast-enhanced MRI [12]. Similar radial enhancement can also be observed in the cerebellum. Spinal cord MRI frequently shows long-segment abnormalities, predominantly involving the central gray matter, with occasional enhancement [3, 12]. In this patient, MRI showed heterogeneous signals spanning T1-T12, characterized by scattered patchy lesions with slightly hyperintense T2, isointense T1 signals, and heterogeneous post-contrast enhancement.

Currently, no standardized diagnostic criteria exist for GFAP-A [13]. Diagnosis primarily relies on integrating clinical manifestations, imaging findings, and positive GFAP antibody detection. In this case, the patient developed clinical signs of myelitis one year after laryngeal cancer diagnosis and treatment. Imaging showed long-segment lesions at T1-T2, involving the central gray matter, with significant enhancement. Spinal cord MRI findings were consistent with previously reported characteristics. Both serum and cerebrospinal fluid GFAP antibody tests were positive at a titer of 1 : 32, confirming the diagnosis of autoimmune GFAP myelitis.

Currently, no established standard treatment plan exists for GFAP-A, with most treatments relying on clinical experience [13]. Most patients respond well to steroid therapy, but some experience relapse or fatal outcomes [13]. High-dose corticosteroid pulse therapy is the primary acute-phase treatment, often combined with plasma exchange and intravenous immunoglobulin. Maintenance therapy typically consists of oral prednisone with gradual dosage tapering [14]. Relapse occurs in approximately 20-50% of cases, often during prednisone tapering [3, 14]. In this case, the patient's symptoms initially improved after acute-phase high-dose corticosteroid pulse therapy. However, symptom exacerbation and peripheral nerve injury – manifested as limb numbness, pain, and decreased tendon reflexes – occurred during dosage tapering. Electromyography and nerve conduction velocity tests were not performed due to the patient and family declining further diagnostic evaluation. In the absence of acute imaging evidence of enhancing lesions, symptoms improved with continued maintenance therapy (dosage tapering) and neurotrophic agent administration. Follow-up showed improvement in numbness, pain, and lower limb weakness, with the patient regaining the ability to walk and perform daily activities independently.

The co-occurrence of GFAP-A and laryngeal cancer poses diagnostic challenges due to the non-specificity of symptoms, increasing the risk of misdiagnosis or underdiagnosis [15, 16]. Postoperative lower limb weakness and bowel-urinary dysfunction may suggest concurrent autoimmune GFAP myelitis in laryngeal cancer patients. Prompt MRI of the brain, cervical, and lumbar spine, combined with cerebrospinal fluid GFAP antibody testing, is crucial for minimizing diagnostic errors. Understanding of the pathogenesis is limited by insufficient biopsy data and the lack of relevant animal model studies. Thus, the mechanisms of GFAP-A and the immunological role of GFAP antibodies remain poorly defined, warranting further research. Diagnostic criteria for GFAP-A, especially in tumor-related cases, remain unestablished, posing a pressing clinical challenge. Current treatments are primarily empiric, highlighting the urgent need for standardized therapeutic protocols.

Conclusions

This case report illustrates that autoimmune GFAP myelitis can occur concomitantly with laryngeal cancer. In patients with lower limb weakness and bowel-urinary dysfunction after laryngeal cancer surgery, differential diagnoses should include autoimmune GFAP myelitis in addition to thoracic/lumbar spinal cord metastases. Prompt MRI of the brain, cervical, and lumbar spine, along with cerebrospinal fluid GFAP antibody testing, is crucial for minimizing diagnostic errors.

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Disclosures

Informed written consent was obtained from the patient for the publication of this case report and related images.

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University, with the ethical code DSK231017. Procedures conformed to the Declaration of Helsinki (1975, revised 2000).

The authors declare no conflict of interest.

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