

## Immune Checkpoint Inhibitor-Associated Transverse Myelitis

### İmmün Kontrol Noktası İnhibitörü ile İlişkili Transvers Miyelit

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#### ABSTRACT

Immune checkpoint inhibitors (ICIs) are highly effective in treating cancer and are increasingly used. Thus, awareness of various complications in the form of immunity-related adverse events is increasing. Transverse myelitis following ICIs is a rare but severe neurological adverse event, and information about this entity is minimal. ICI-associated transverse myelitis should be considered a rapid and comprehensive differential diagnosis after evaluating infective, metabolic, or other inflammatory-autoimmune pathologies. After diagnosis, early immunomodulation is required through intravenous high-dose methylprednisolone, IVIg, or plasmapheresis. It should be kept in mind that different etiologies may coexist or a superimposed condition may cause each other, and concurrent treatment should not be delayed. Further studies are needed to investigate the neurological manifestations that may develop in association with these therapies further and help establish guidelines for their management. In this case report, a rare case of ICI-associated transverse myelitis in a 62-year-old male patient was presented.

**Keywords:** Immune checkpoint inhibitor; adverse event; transverse myelitis.

#### ÖZ

İmmün kontrol noktası inhibitörleri (immune checkpoint inhibitors, ICIs) kanser tedavisinde oldukça etkilidir ve giderek daha fazla kullanılmaktadır. Bu nedenle, bağışıklıkla ilişkili advers olaylar şeklinde çeşitli komplikasyonlara ilişkin farkındalık artmaktadır. ICI'ları takiben gelişen transvers miyelit, nadir ancak ciddi bir nörolojik advers olaydır ve bu antite hakkındaki bilgiler çok sınırlıdır. Enfektif, metabolik veya diğer enflamatuvar-otoimmün patolojilerin değerlendirilmesinden sonra hızlı ve kapsamlı bir ayırıcı tanı olarak ICI kaynaklı transvers miyelit dikkatle düşünülmelidir. Tanıdan sonra, intravenöz yüksek doz metilprednizolon, IVIg veya plazmaferez şeklinde erken immünomodülasyon gereklidir. Farklı etiyolojilerin bir arada bulunabileceği veya üst üste binen bir durumun birbirine neden olabileceği akılda tutulmalı ve eş zamanlı tedavi geciktirilmemelidir. Bu tedavilere bağlı olarak gelişebilecek nörolojik bulguların daha fazla araştırılması ve bunların yönetimine ilişkin kılavuzların oluşturulmasına yardımcı olmak için daha fazla çalışmaya ihtiyaç vardır. Bu olgu sunumunda, 62 yaşında bir erkek hastada, nadir görülen bir ICI ile ilişkili transvers miyelit vakası sunulmuştur.

**Anahtar kelimeler:** İmmün kontrol noktası inhibitörü; advers olay; transvers miyelit.

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#### INTRODUCTION

Immune checkpoint inhibitors (ICIs) may cause immune-related adverse events (1,2). ICI-associated transverse myelitis should be carefully considered as a rapid and comprehensive differential diagnosis after evaluation of infective, metabolic, or other inflammatory-autoimmune pathologies. On the other hand, it should be remembered that different etiologies may coexist, overlapping conditions may cause

each other, and concurrent treatment should not be delayed. This case report aimed to present a rare but confusing case of ICI-associated transverse myelitis.

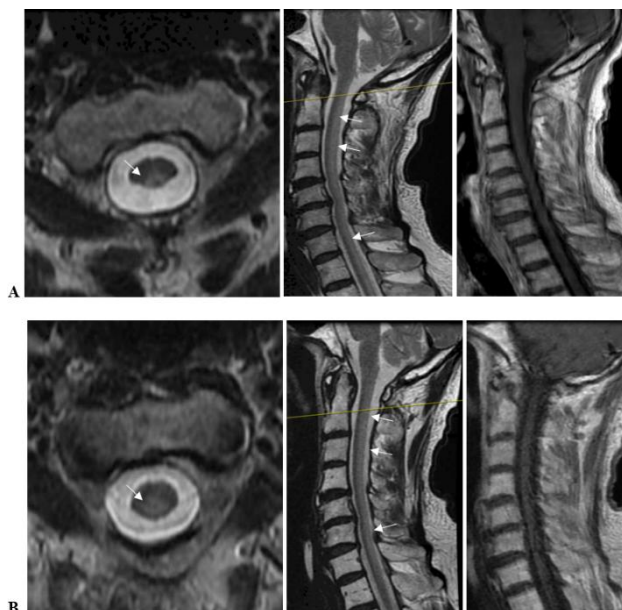
### CASE REPORT

A 62-year-old male was diagnosed with small cell lung cancer (SCLC) with lymphatic and vertebral metastases one year ago. He was treated with seven cycles of etoposide and carboplatin (3 doses daily per cycle) and currently two doses of atezolizumab. One month after the second dose of atezolizumab, he presented with subacute onset bilateral lower extremity weakness, urinary overflow incontinence, numbness in all extremities, and involuntary contractions in upper extremities. On examination, there were proximal (4/5) and distal (3/5) bilateral symmetrical upper extremity and bilateral lower extremity (right; 3/5, left; 2/5) weakness, sensory ataxia, spasticity in all extremities, loss of bilateral deep tendon reflexes and loss of deep sensation (vibration and joint position). He was limited to a wheelchair and self-catheterization.

Cervical and thoracic spine magnetic resonance imaging demonstrated symmetrical T2 signal hyperintensity confined to the lateral tracts without contrast enhancement from C1 to T11 and a T1 hypointense lesion of the T9 and T11 vertebral body with irregular T2 signal and contrast enhancement (Figure 1). EMG demonstrated a polyneuropathy syndrome in the subacute period with axonal damage in which sensory and motor fibers were affected. There was no response in bilateral lower and upper extremities' sensory evoked potentials (SEPs). In visual evoked potentials (VEPs), the P100 wave could not be obtained on the left, and there was a prolongation of P100 wave latency on the right. Routine laboratory examination, hemogram, thyroid function tests, serum cobalamin, folate, and methylmalonate (0.11 nmol/ml, NV 0-0.4) were within the normal range. No lymphocytes or malignant cells were

detected in the CSF analysis, and the glucose level was in the normal range proportionally to serum (63/102 mg/dl). A slight increase was in protein (46.2 mg/dl, NV 15-45), and LDH (27 U/L, NV 10-19). Serum antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG), serology for neurotropic viruses (including CMV, HIV, EBV, HBV, HCV, and HSV1-2), rheumatological screening tests (including ANA, thyroid antibodies, beta2glycoprotein, p-ANCA, rheumatoid factor, c-ANCA, anti-cardiolipin, celiac antibodies), serology for *Brucella*, *Borrelia burgdorferi*, and *Treponema pallidum*, paraneoplastic panel antibodies (including anti-NMDR, AMPA1, AMPA2, CASPR2, LGI1, Amphiphysin, GABARB1/B2, CV2, PNMA2, Ri, Yo, Hu, Recoverin, Titin, Zic4, GAD65, TRAB, SOX1), and brain MRI were normal. Serum copper level (53 µg/mL, NV 70-140) and ceruloplasmin (193 mg/L, NV 200-600) were slightly below normal limits, and serum zinc concentration mildly exceeded the reference range (159 µg/L, NV 73-127). The copper level (4.2 µg/24h) in 24-hour accumulation urine was average. The patient denied any history of zinc abuse. Total blood count did not reveal anemia or cytopenias.

There was minimal improvement in neurological examination (10% improvement in upper limb muscle strength loss) after five cycles of every other day therapeutic plasma exchange for transverse myelitis at initial presentation. Although the amount of copper excreted in urine was normal, serum copper and ceruloplasmin levels were borderline low. So, 8 mg/day oral copper supplementation and zinc-poor diet were administered for eight months. Routine laboratory tests, thyroid function tests, serum cobalamin, folate, and methylmalonate were within the normal range at month eight of replacement therapy. Electrophysiological tests were repeated. In VEP, in addition to prolonged P100 latency on the right side, prolonged conduction could be obtained on the left side (amplitude; 5.28/4.99 µv, latency; 131/133 ms, respectively). While there was no conduction on SEP eight months ago, bilateral prolonged P40 wave latencies (44 and 49.2 ms) and normal p60 waves in the lower extremities, and prolonged N20 and P25 wave latencies (20.8 and 24.6 ms) in the upper extremities on the left side, while no response was obtained on the right side. No change was observed in the control EMG results, neurological examination, and control MRI. Ceruloplasmin, serum copper, and urinary copper excretion in 24 hours were within normal limits (277 mg/L, 110 µg/mL, 4.8 µg/24h, respectively). Serum zinc level decreased after dietary administration (145.4 µg/L), and 24-hour urinary zinc excretion was within normal limits (910 µg/24h, NV 200-1300). With these results, exogenous zinc intake was ruled out. After all exclusion, despite the improvement in laboratory values and electrophysiological tests, the absence of difference in neurological examination and spinal MRI concluded that ICI-associated transverse myelitis was superimposed with possible copper deficiency.



**Figure 1.** A) Cervical spinal magnetic resonance imaging (MRI) at initial presentation (first month of complaint onset), axial T2, sagittal T2, and sagittal contrast-enhanced (C+) T1, respectively. arrows; T2 hyperintense longitudinally extensive transverse myelitis (LETM); B) Spinal MRI repeat at 8<sup>th</sup> month, axial T2, sagittal T2, and sagittal C+ T1, respectively. arrows; LETM without change

### DISCUSSION

The risk of neurological complications is high with the use of ICI. Neurological side effects constitute 1-5% of the side effects related to ICIs. Adverse events may develop with the impact of other organ systems, as they show their effect by increasing the endogenous immune response. In addition to myelitis, hypophysitis, myasthenia gravis,

encephalitis, meningitis, neuromyelitis optica spectrum disorder, vasculitis, and polyneuropathy have been reported as neurological adverse effects (1,2). They are usually severe and carry a risk of long-term disability or death (3). Symptoms typically occur within 6 to 12 weeks of the onset of ICI but can sometimes occur immediately after initiation of the drug or months (2-17 months) after discontinuation of ICI (4-6). Myelitis associated with ICPs is usually in the long, lower cervical, and thoracic segments, with an expansive, punctate, or patchy enhanced or unenhanced appearance (6). It has been reported in the literature after durvalumab, nivolumab, pembrolizumab, and atezolizumab in patients with SCLC, non-SCLC, melanoma, and hepatocellular carcinoma (7,8). A slight increase in isolated bos protein is generally detected (6,8). Although an excellent response to steroid or plasmapheresis treatments has been reported, it is clinically variable, poor response to treatment, and permanent disability may occur (6,7,9). The case of myelitis after atezolizumab is rarely mentioned in the literature. Transverse myelitis has been reported after atezolizumab in one issue of metastatic SCLC and after its combination with bevacizumab in one case of hepatocellular carcinoma (5,10).

The two main manifestations of copper deficiency are bone marrow and the neurological system. Gastrointestinal surgery, zinc overload, malabsorption, long-term parenteral nutrition, and alcohol use are the main risk factors, respectively (11). Copper deficiency myelopathy usually presents as chronic progressive myelopathy (12). Initially, most patients (78%) had anemia/cytopenia (13,14). In a clinically compatible case, one or more risk factors and cytopenia may suggest copper deficiency myelopathy. Copper levels may fall below the normal range with plasmapheresis treatment or in the presence of malignancy; required for tumor growth or development of metastases (15,16).

Subacute onset, absence of bone marrow involvement, lack of risk factors, and serum copper and ceruloplasmin levels close to the minimal limit suggested that this was ICI-associated myelitis rather than metabolic myelopathy or polyneuropathy. This was confirmed by partial clinical improvement with plasmapheresis treatment in the early phase and no clinical change with eight months of copper replacement in the late phase. In conclusion, in this case, in which atezolizumab treatment was not continued during the follow-up period, it was concluded that the leading cause was ICI-associated subacute transverse myelitis clinic and mild copper deficiency secondary to malignancy overlapped.

## CONCLUSION

Immune checkpoint inhibitors (ICIs) are highly effective in treating cancer and are increasingly used. Thus, awareness of various complications in the form of immunity-related adverse events is increasing. Transverse myelitis following ICIs is a rare but severe neurological adverse event, and information about this entity is minimal. ICI-associated transverse myelitis should be carefully considered as a rapid and comprehensive differential diagnosis after evaluation of infective, metabolic, or other inflammatory-autoimmune pathologies. After diagnosis, early immunomodulation is

required through intravenous high-dose methylprednisolone, IVIg, or plasmapheresis. On the other hand, it should be kept in mind that different aetiologies may coexist or a superimposed condition may cause each other, and concurrent treatment should not be delayed. Further studies are needed to investigate the neurological manifestations that may develop in association with these therapies further and help establish guidelines for their management.

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