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LETTER TO THE EDITOR

Acute transverse myelitis and paralysis in a kidney–pancreas recipient

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Acute transverse myelitis (ATM), a group of neurologic disorders with an incidence of one to four cases per million people per year, is characterized by focal inflammation of the spinal cord resulting in sensory, motor, and autonomic dysfunction. ATM may be caused by infection, spinal cord infarction, pre-existing inflammatory disease (e.g., SLE), or *de novo* autoimmunity (idiopathic) [1].

Acute transverse myelitis typically presents with thoracic sensory loss and focal acute inflammation of the spinal cord visible on MRI. Examination of lumbar cerebrospinal fluid (CSF) reveals significant pleocytosis without evidence for infection. Motor loss involves the lower extremities bilaterally but can include the upper extremities in severe cases. These symptoms reach peak severity between 4 h and 21 days after onset [2].

The diagnosis of ATM includes ruling out radiation exposure, vascular events, connective tissue disorders, and infection. MRI of the brain and spine is necessary to rule out compressive etiologies. Laboratory studies of CSF is required to rule out syphilis, Lyme disease, mycoplasma, human immunodeficiency virus, human lymphotropic virus-1, or other viral infection. CSF examination may detect proteins that may aid in making the diagnosis and predicting the severity of ATM [1–4].

Treatment for autoimmune ATM includes high-dose steroids, antimetabolites, and plasmapheresis [5]. Approximately equal proportions of ATM patients recover with little neurologic deficit, moderate disability (ambulation with assistance), or permanent severe disability [2–4,6].

Our patient is a 35-year-old African-American male with Type I diabetes and a strong family history of autoimmune diseases. He underwent deceased donor simultaneous kidney and pancreas transplantation with T-cell depleting rabbit anti-thymocyte globulin (rATG) induction (total of 7 mg/kg) with methylprednisolone (total of 15 mg/kg). Maintenance immunosuppression consisted of mycophenolate mofetil and tacrolimus started on postoperative day (POD) 1 and 5 respectively.

On POD 10, he developed a urinary tract infection with *Enterobacter aerogenes* for which ciprofloxacin was initiated. On POD 16, he developed a right lower lobe pneumonia, was intubated, and treated with imipenem-cilastatin and linezolid. Continued fever after resolution of pneumonia led to exploratory laparotomy without significant findings.

On POD 25, physical examination revealed poor muscle tone in both upper and lower extremities. An MRI showed normal brain and lumbar spine but increased T2 signal of the spinal cord from C5–6 to T4 consistent with myelitis (Fig. 1a and b). CSF revealed a greatly elevated protein level (709 mg/dl) and subsequent CSF cultures and antigen testing were all negative. Intravenous methylprednisolone (500 mg b.i.d.) was started and initially the patient defervesced, but within 4 days he was persistently febrile (>38 °C) despite wide-spectrum antibiotics and high-dose steroids. Multiple follow-up bacterial cultures, virologic and serologic studies were negative.

On POD 27, the patient appeared to improve somewhat and was extubated. Neurologic examination revealed a lack of pinprick sensation from chest to thighs, inability to move lower extremities, and gross but not fine motor movement in upper extremities. The patient remained febrile, and a follow-up MRI performed 7 days later (Fig. 1c and d) showed significant progression. A follow-up lumbar puncture showed decline of CSF protein to 243 mg/dl and despite continued negative microbial, viral, and serologic studies the patient remained febrile.

Follow-up MRI on POD 52 (Fig. 1e and f) showed progression of transverse myelitis to T10-11 and an electromyographic study showed severe axonal sensorimotor polyneuropathy. Plasmapheresis was initiated every other day for a total of seven treatments. He reported temporary improvement in sensation in his abdomen and legs while receiving plasmapheresis. After his last treatment, high-dose steroids were restarted and subsequently tapered to 5 mg of oral prednisone daily.

A repeat MRI on POD 67 showed no further progression or resolution of the transverse myelitis.

The patient eventually became afebrile and was discharged 81 days after transplantation with a T2–3 complete paraplegia and partial involvement of the left C8–T1 dermatomes and myotomes. To date, the patient has shown no further recovery despite a long course of steroids. MRI performed 8 months later showed extensive

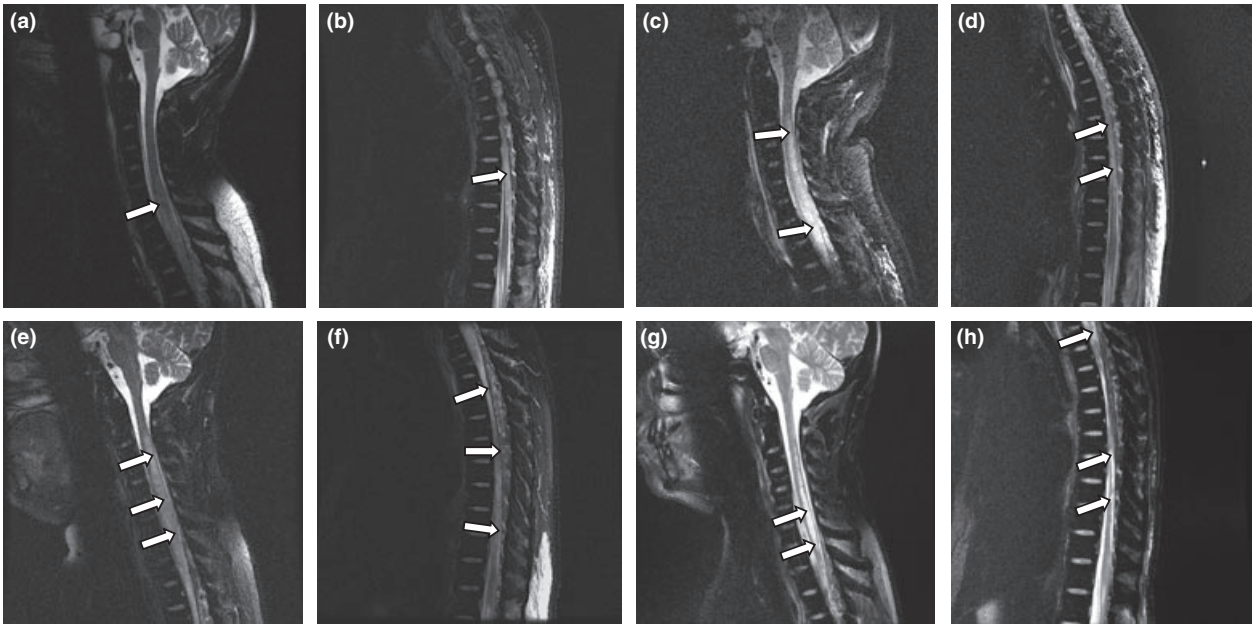

Figure 1 Sagittal MRI scans of cervical and thoracic spines utilizing T2 fat-saturated technique. Initial MRI of the cervical (a) and thoracic (b) spinal cord showing increased T2 signal and enhancement primarily involving white matter from C5–6 to T3–4. Follow-up MRI scans on POD 32 (c,d) and POD 52 (e,f) demonstrate moderate progression of edema, both inferiorly and superiorly, of the cervical (c,e) and thoracic (d,f) spinal cords. Follow-up MRI (g,h) 8 months later shows spinal cord edema has decreased, being confluent from C2–3 to C7–T1 and patchy throughout the atrophic thoracic spinal cord.

spinal cord atrophy beginning at C7–T1 and extending distally (Fig. 1g and h).

Acute transverse myelitis belongs to a spectrum of CNS disorders thought to result from autoimmunity and typified by acute neurologic deterioration associated with inflammatory cell infiltrates and demyelination. Treatment has been directed at preventing permanent neurologic damage by suppressing the immune system with intravenous high-dose steroid therapy. Retrospective analyses show a trend toward neurologic improvement with this treatment, especially if initiated early [4]. Plasma exchange is used when steroid treatment fails or when patients are unable to walk [2,5,6]. In recurrent ATM, chronic immunomodulatory therapy with azathioprine, methotrexate, or mycophenolate mofetil is commonly utilized [2]. Most authors agree that treatment success is based on early initiation [6].

We have found no other reports of autoimmune ATM developing during high-dose immunosuppression, and one might think that it would not appear under such conditions. However, alemtuzumab and rATG have been associated with autoimmune thyroiditis and Hashimoto's encephalitis [7,8]. In these cases, autoimmunity was hypothesized to be attributable to expansion of residual autoreactive memory T-cell clones [9]. In the Hashimoto's encephalopathy case, the patient was enrolled in a clinical trial of rATG induction with early steroid withdrawal followed by calcineurin-inhibitor discontinuation, a combination that could potentially lower the threshold for new autoimmune disease to develop [8,10]. In this instance, the abrupt onset of autoimmunity suggests the expansion of a pre-existing autoreactive memory T-cell clone, perhaps precipitated by increased innate immune activity resulting from severe infection [11].

It is striking that our patient developed ATM soon after induction and while receiving maintenance immunosuppression (tacrolimus and mycophenolate mofetil). In an animal model of chronic experimental autoimmune encephalomyelitis, impaired Treg response was critical for development of chronic autoimmune disease [12]. Whereas rATG can provoke expansion of the Treg phenotype *in vitro* (without complement), extensive lymphocyte lysis would prevent this *in vivo* [13–15].

We hypothesize that surviving memory T cells, after Treg cells are reduced by antibody-mediated T-cell depletion, could provide a setting for the development of *de novo* autoimmunity, if the number of surviving regulatory T cells is insufficient to inhibit the expansion of an autoreactive T-cell clone during homeostatic repopulation [9]. The benefits of lytic immunosuppression induction and subsequent maintenance minimization remain controversial and indeterminable

without prospective randomized clinical trials in combination with related immunologic studies.

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