Journal of Neuroimmunology 336 (2019) 577028

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short Communication

Successful combined treatment with thymectomy, rituximab and tocilizumab for severe thymoma-associated multi autoimmune syndrome

Olafur Sveinsson[a,b,*], Fredrik Piehl[a,b], Oskar Aspegren[c,d], Max Albert Hietala[a]

[a] Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
[b] Department of Clinical 7 Neuroscience, Karolinska Institutet, Stockholm, Sweden
[c] Department of Pathology, Karolinska University Hospital, Stockholm, Sweden
[d] Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Keywords:
Thymoma-associated multi-autoimmune syndrome
Thymoma
Thymectomy
Rituximab
Tocilizumab

ABSTRACT

We present a 53-year-old woman who presented simultaneously with acute inflammatory demyelinating polyneuropathy, Graves' disease, leukocytoclastic vasculitis, elevated acetylcholine antibody receptor antibodies and a mediastinal mass. Thymectomy was performed and revealed a type A thymoma and the clinical picture and paraclinical findings were consistent with a thymoma-associated multi-autoimmune syndrome (TAMA). Beside prednisolone and plasmapheresis, the patient was treated with tocilizumab and rituximab. After surgical and immunomodulatory treatment with tocilizumab and rituximab the patient's condition slowly started to improve. TAMA is associated with a spectrum of autoantibodies and immune-mediated damage to multiple organs. Even if thymectomy is crucial for long term prognosis, aggressive immunomodulation should be considered early in the disease course, especially in cases showing involvement of the peripheral and/or central nervous system.

1. Case report

A 53-year-old woman, smoker with no previous medical history, presented at the emergency room (ER) with skin rashes and progressive muscle weakness in her right leg since a few weeks. She had vesicular papules on the back of her neck and right leg, which was interpreted as herpes zoster and treatment with herpetic antivirals was initiated. Due to lack of response, she sought emergency care again and a preliminary diagnosis of lumbosacral plexus neuritis was made. However, cerebrospinal fluid (CSF) analysis did not reveal pleocytosis, CSF albumin levels were only mildly elevated (435 mg/L, reference < 400 mg/L) and routine microbiological tests for bacteria, fungi and neurotropic viruses were negative. CSF-neurofilament light (NfL) levels were very high (> 60,000 ng/L, ref. < 890 ng/L), indicating severe ongoing axonal degeneration. Her clinical status included bilateral paraparesis and absence of tendon reflexes, albeit no sensory involvement. Neurophysiological tests were indicative of an acute motor axonal neuropathy (AMAN), showing both axonal damage and demyelination with multifocal blocks. Testing for antibodies against gangliosides was negative. An extensive panel of other autoimmune antibodies was also negative. Magnetic resonance imaging (MRI) of the spinal cord showed gadolinium enhancement of the nerve roots, providing additional support for an AMAN. MRI of the brain and EEG were unremarkable. Based on these findings, she was treated with intravenous immunoglobulins (IVIG) for five days (2 g/kg body weight).

Further clinical and laboratory examinations revealed tremor, weight loss and hyperhidrosis, as well as suppressed thyroid stimulating hormone (TSH: < 0.02 mE/L, ref. 0.3–4.2 mE/L) and elevated free thyroxine (T4: 44 pmol/L, ref. 12–22 pmol/L) and free triiodothyronine (T3: 13 pmol/L, ref. 3.1–6.8 pmol/L), consistent with the diagnosis of Graves' disease. She also tested positive for thyroid peroxidase (TPO: 149 kE/L, ref. < 34 kE/L) and thyrotropin receptor antibodies (TRAbs: 13 E/L, ref. < 1,8 E/L). Additional treatment with thiamazole, levothyroxine and propranolol was initiated.

Furthermore, she also displayed a lupus-like rash that in skin biopsy revealed signs of small vessel leukocytoclastic vasculitis. Blood tests were strongly positive for anti-nuclear antigen (ANA ≥ 1:320 both homogenous and nucleolar pattern) with high levels of antibodies for doubled stranded DNA (dsDNA: 190 IE/mL, ref. < 10 IE/mL). Myeloperoxidase antibodies were mildly elevated (MPO: 1.5 E/mL, ref. < 1 IE/mL). Because of presumed systemic lupus erythematosus (SLE)-associated vasculitis, she was treated with high dose methylprednisolone (1 g/d) for five days and then 60 mg prednisolone daily. Interestingly, acetylcholine antibody receptor antibodies were also elevated (1.6 nmol/L, ref. < 0.2 nmol/L), although typical symptoms of myasthenia gravis, such as eye muscle involvement, were absent.

* Corresponding author at: Department of Neurology, Karolinska University Hospital, 171 76 Stockholm, Sweden.
E-mail address: olafur.sveinsson@sll.se (O. Sveinsson).

https://doi.org/10.1016/j.jneuroim.2019.577028
Received 2 August 2019; Received in revised form 21 August 2019; Accepted 22 August 2019

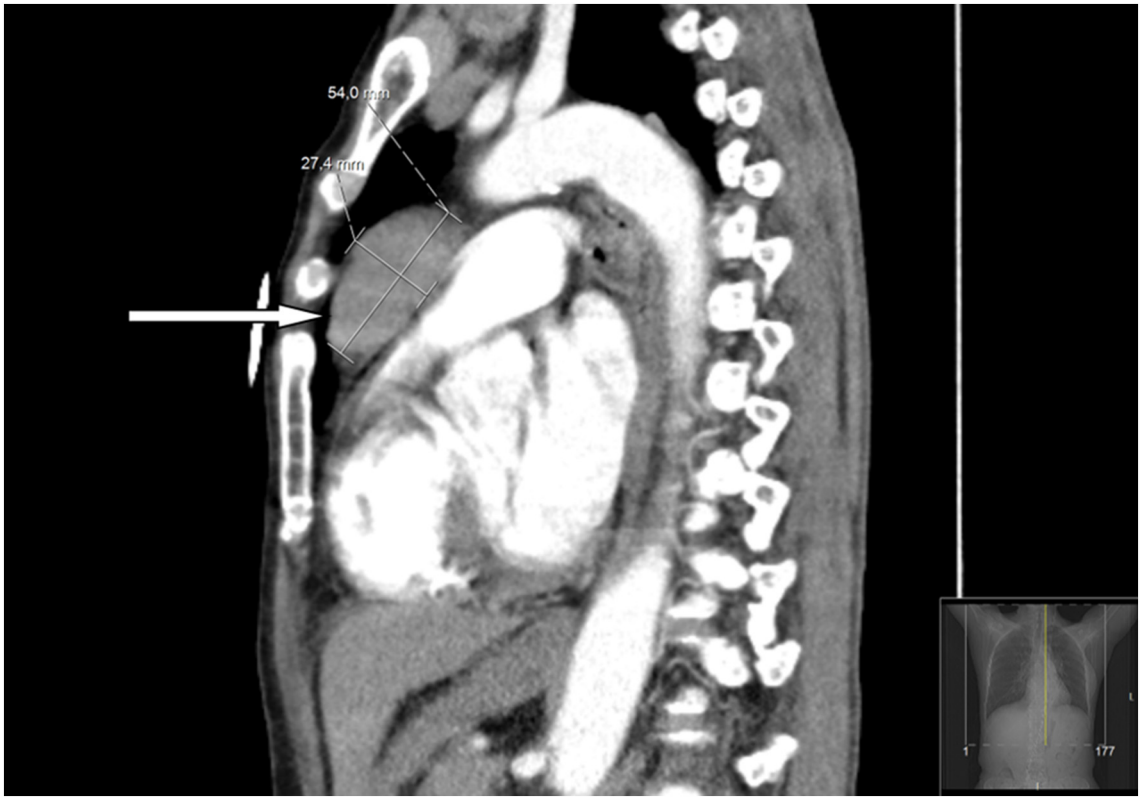

Fig. 1. CT thorax showing the mediastinal mass (arrow) (5,4 × 4,0 × 2,5 cm).

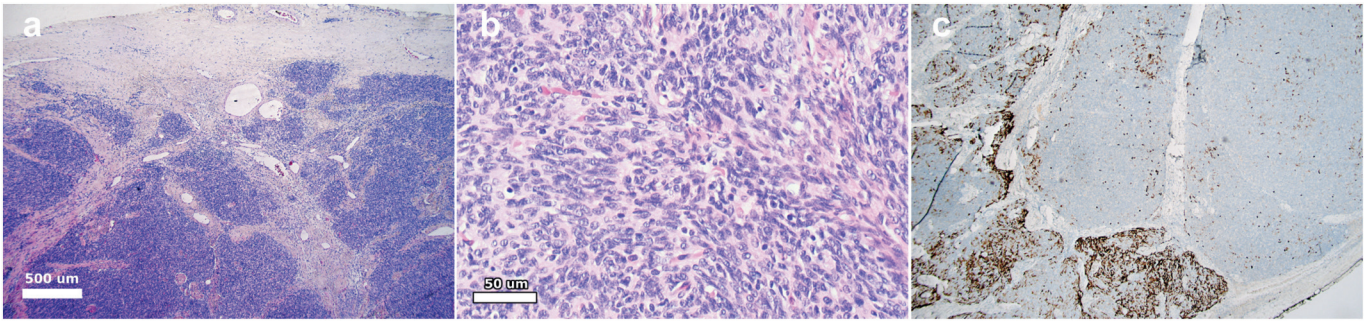

Fig. 2. Microscopic figures showing the morphology of the thymoma type A. a) At low power, a thick fibrous capsule is seen along the border of a well circumscribed tumor with internal fibrous septations that intersect one another at acute angles. Hematoxylin and Eosin. b) At high power, the tumor is composed of a population of neoplastic epithelioid cells having spindle and oval shape, without significant nuclear atypia and accompanied by a few non-neoplastic lymphocytes. Hematoxylin and Eosin. c) Immunohistochemical stain with anti-CD20 antibodies showing strong and patchy staining within the tumor cell population.

Within weeks of hospital care, her clinical condition deteriorated dramatically because of respiratory failure (neuromuscular weakness and pneumonia), which necessitated intensive care with invasive ventilation. Before she was put on a ventilator her first arterial blood gas on 6 L of oxygen showed hypoxia (pO2 7.6 kPa, ref. > 10), saturation 90% but normal pCO2. CSF-NfL levels had now increased to 93,000 ng/L, suggesting massive neuroaxonal degeneration. The diagnostic work-up of her systemic inflammatory condition included a computerized tomography of abdomen and thorax, which revealed a mediastinal mass (Fig. 1). Thymectomy was performed and the specimen was sent for histopathological analysis. Macroscopically, the tumor was lobulated, completely encapsulated and measured 5,4 × 4,0 × 2,5 cm. Histology showed a well circumscribed epithelial tumor, surrounded by a thick fibrous capsule without evidence of infiltration or tumor necrosis (Fig. 2a). The tumor cells were spindle-shaped, uniform with bland nuclei and arranged in a swirling pattern, with only very few small and reactive interspersed lymphoid cells (Fig. 2b). The mitotic count was < 1 per 10 high-power fields (HPFs). On immunostaining, the tumor cells showed diffuse cytokeratin reactivity and strong, but patchy CD20 reactivity (Fig. 2c). Staining for terminal deoxynucleotidyl transferase (TdT) revealed nuclear expression only in sporadic and isolated immature T lymphocytes (< 1% of the lymphocytic population) (not shown). Expression of the proliferation marker ki67/MIB-1 was very low (not shown). The tumor was diagnosed as a thymoma type A in accordance with WHO classification of tumors of the thymus (4th edition, 2015).

The clinical picture and paraclinical findings were consistent with a thymoma-associated multi-autoimmune syndrome (TAMA). After thymectomy, prednisolone was reduced from 60 mg/d to 40 mg/d and she received plasmapheresis with five plasma exchanges. Additionally, she was treated once with tocilizumab, an interleukin-6 blocker, (8 mg/kg body weight) and rituximab (500 mg single dose) because of the CD20 positivity in her thymoma. After surgical and immunomodulatory treatment, her condition slowly started to improve and CSF-NfL levels

decreased to 67,000 ng/L.

After three weeks of intensive care, she was transferred to a regular neurology ward, and a few weeks later to a neurological rehabilitation clinic. Two months after surgery, CSF-NfL levels had fallen to 24,500 ng/L and prednisolone was tapered off, without further need of other immunomodulatory drugs. Now, a year after surgery she is still paraparetic but can walk some steps with assistance. Moreover, CSF-NfL levels have decreased to 2320 ng/L. The previous mentioned multiple autoantibodies were still detected after treatment, albeit in lower titers.

2. Discussion

TAMA is a newly defined, rare paraneoplastic syndrome in patients with thymoma. It usually manifests as a graft versus host disease (GvHD)-like condition with symptoms and clinical findings consistent with multi-organ involvement, usually with a poor prognosis (Fukushima et al., 2017 and Solimani et al., 2019). Whilst the histomorphological findings in the target organs may be indistinguishable from those in the classical form of GvHD, the absence of grafted lymphocytes necessitates the term “GvHD-like”. Although the pathogenesis remains incompletely understood, defective T cell immune selection within the dysfunctional neoplastic epithelial environment of the thymoma seems plausible (Fukushima et al., 2017). Absent or decreased autoimmune regulator (AIRE) protein in neoplastic thymic epithelial cells may lead to incomplete elimination of self-reactive T-cells that escape into the peripheral circulation and drive the GvHD-like pathology (Offerhaus et al., 2007). Beside thymoma, multiple autoimmune syndromes have been described in association with other tumors, such as neuroblastoma (Amini et al., 2016).

The TAMA cases documented to date have shown a female predominance, with a mean age of 47 years at presentation (Fukushima et al., 2017; Offerhaus et al., 2007; Kornacki et al., 1995; Sader et al., 2002). Clinical features of paraneoplastic autoimmunity appear before, after, or synchronously with the diagnosis of thymoma. Most cases have been associated with malignant thymoma. TAMA patients frequently succumb to infective complications secondary to immune suppression due to either the paraneoplastic syndrome or to chemotherapy administered for the thymoma (Fukushima et al., 2017). However, TAMA survivors, with signs and symptoms similar to those in our case have been previously described in the literature (Kung et al., 2009). The patient described in this case report showed a surprisingly good general recovery despite her paraparesis due to AMAN, which in general, has a worse prognosis than AIDP (Kuwabara and Yuki, 2013). CSF-NfL levels peaked at very high concentrations, consistent with massive neuroaxonal degeneration, which is associated with a poorer long-term outcome in AIDP (Axelsson et al., 2018). Even if MRI of brain and spinal cord was devoid of focal abnormalities, we cannot exclude disease involvement of the central nervous system (Zetterberg, 2016).

Collectively, it is important to consider thymus pathology in cases presenting with multiple autoimmune disorders simultaneously, particularly since TAMA is a potentially treatable condition. However, since the clinical effects of thymectomy are delayed in MG (Wolfe et al., 2016), and most likely also in TAMA, it is important to consider faster acting treatments. High dose corticosteroids combined with plasma exchange and/or immunoglobulins are recommended in cases of severe antibody-mediated neuroinflammation (Gastadli et al., 2016). Based on clinical experience we chose to administer both tocilizumab and rituximab to target the underlying immunopathogenesis in two different ways (Sveinsson et al., 2017). Notably, a placebo-controlled randomized trial of anti-IL 6 for patients with neuromyelitis optica spectrum disorders has provided class A evidence for clinical efficacy in an antibody-mediated neurological condition (Yamamura, 2018). In addition, we have previously reported two cases of rituximab-refractory myasthenia gravis that responded to tocilizumab (Jonsson et al., 2017). While we cannot rule out that the clinical improvement seen in this case was independent of the immunomodulatory treatment administered, the poor prognosis generally associated with TAMA and the rapid worsening of this patient's condition prior to surgery along with the timing of immunotherapy provide some support for the value of aggressive immunomodulatory treatment early on.

In summary, TAMA is associated with a spectrum of autoantibodies and immune-mediated damage to multiple organs. In this setting, thymic neoplasia needs to be ruled out. Even if thymectomy is crucial for long term prognosis, aggressive immunomodulation should be considered early in the disease course, especially in cases showing involvement of the peripheral and/or central nervous system. To the best of our knowledge, the combination of rituximab and tocilizumab has not previously been reported in similar cases.

Funding

No funding.

Declaration of Competing Interest

OS, OA, MAH do not report any conflicts of interest. FP has received research grants from Biogen, Genzyme, Merck KGaA and Novartis, and fees for serving as Chair of DMC in clinical trials with Parexel, all outside the submitted work.

Acknowledgements

The reporting of clinical data was approved by the patient.

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