An unusual case of stiff person syndrome: paraneoplastic or autoimmune?

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Introduction: stiff person syndrome (SPS) is a rare disorder characterized by fluctuating muscle rigidity, painful spasms and difficulty walking[1]. Conventionally, three variants of SPS have been described: autoimmune, paraneoplastic, and cryptogenic. Autoimmune SPS is defined by auto-antibodies (autoAb) positivity, mainly anti-glutamic acid decarboxylase (GAD65) or α_1-subunit of glycine receptor (GlyR), and is associated with other autoimmune disorders. Conversely, paraneoplastic SPS encompass all cases emerging in the context of cancer[2], often being associated with anti-amphiphysin autoAb. We describe a case of SPS with associated multi-antigen autoimmunity and thymus hyperplasia, and results after thymectomy.

Methods: a 42-years-old woman was admitted at the Neurological department of our Hospital with a 5-years-long history of progressive axial and legs stiffness, leading to hyperlordosis and difficulty walking, and muscular spasms. She previously received long-term immunotherapy, with poor and not persistent clinical response. The patient underwent neurophysiological investigation, and subsequently computed tomography (CT) and total-body positron emission tomography (PET) scans, breast and trans-vaginal ultrasound to search for occult cancers. In parallel, an extensive autoimmune screening was performed, together with esophago-gastro-duodenoscopy and thyroid ultrasound.

Results: a diagnosis of SPS was made, based on clinical and neurophysiological parameters. Paraneoplastic screening resulted negative. We detected a high titre of anti-GAD65 autoAb in serum, highlighting an autoimmune form of SPS. Positivity for anti-gastric parietal cells, anti-thyroglobulin, and anti-thyroid peroxidase autoAb was also found, along with the evidence of chronic inflammation in stomach and thyroid. Total body PET-scans outlined a metabolically active enlarged residual thymus gland (**Figure 1**). A concomitant myasthenia gravis was excluded.
After repeated ineffective plasmapheresis, a video-thoracoscopic thymectomy was performed, with histological demonstration of true thymic hyperplasia. Surgery leads to marked reduction of neurological symptoms, without any difference in serum antibodies titres.
Unfortunately, clinical beneficial lasted a few months, then the patient relapsed, and immunosuppressive therapy with Rituximab was started.
Biochemical and neurophysiological data of the patient at admission are summarized in **table 1** and **table 2**.

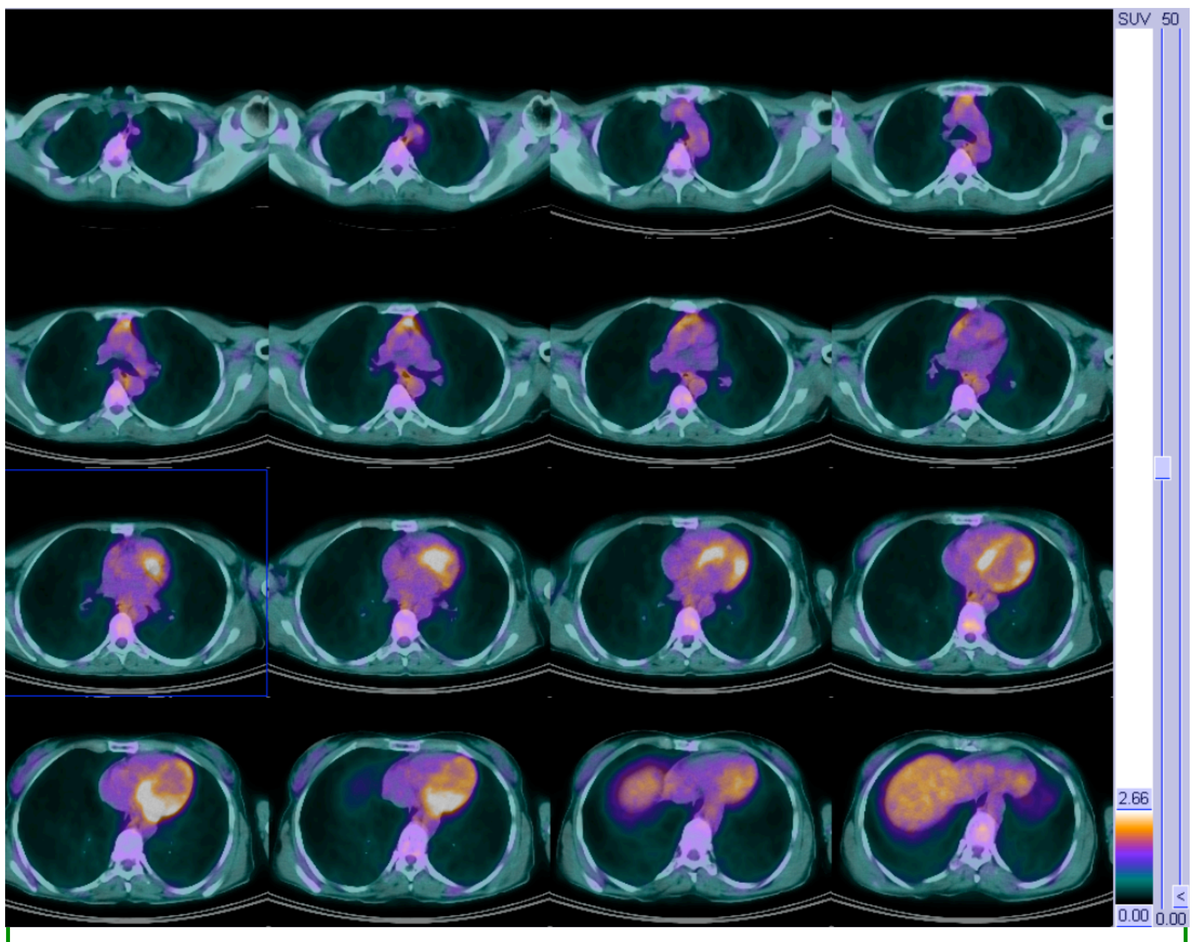

Figure 1: ^{18}F-fluorodeoxyglucose-positron-emission tomography (^{18}F-FDG-PET) scans of the chest: increased glucose-uptake in the thymus area (SUV max 3.3) corresponding to a metabolically active enlarged residual thymus gland.

Discussion: in SPS high titres of anti-GAD65 autoAb can trigger multi-antigen autoimmunity, as observed in our patient. Nevertheless, autoAb' titre doesn't vary with clinical response to treatment and the pathogenetic role remains unclear[2], underlining the need of further investigations inside SPS pathogenesis. An association between SPS and thymus cancer (both benign and malignant) have been previously described, with good results after surgery[3]. We here described a case of autoimmune SPS associated with true thymus hyperplasia without characteristics of malignancy. Despite other previously reported cases, we experienced a limited and not persistent clinical response after thymus resection.

Conclusion: we presented the first autoimmune case of SPS with concomitant multi-antigen autoimmunity, and associated true thymus hyperplasia, with no response after thymectomy.

Anti GAD65 autoAb	+	**Anti TPO autoAb**	+
Anti GlyR autoAb	-	**Anti GPC autoAb**	+
Anti amphiphysin autoAb	-	**Anti AchR Anti Musk autoAb**	-
Anti TG autoAb	+	**CSF OB**	+

EMG showing continuous muscle motor unit firing in stiff muscles	+
EMG with repetitive nerve stimulation test and SF-EMG suggestive of MG	-

Table 1: serological results of autoimmune screening performed at admission [GAD65: glutamic acid decarboxylase; GlyR: α_1-subunit of glycine receptor; TG: thyroglobulin; TPO: thyroid peroxidase; GPC: gastric parietal cells; AchR: acetylcholine receptor; Musk: muscle specific kinase; CSF OB: cerebrospinal fluid oligoclonal bands].

Table 2: neurophysiological exams conducted at admission [EMG: electromyography; SF-EMG: single-fiber EMG; MG: myasthenia gravis].

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